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SECRETED PROTEINS AND NUCLEIC ACIDS ENCODING THEM

Related Application Information

This application is a continuation-in-part of application serial number 09/164,169, filed October 2, 1998, which is a continuation-in-part of application serial number 09/164,220, filed September 30, 1998.

Background of the Invention

Many secreted proteins, for example, cytokines and cytokine receptors, play a vital role in the regulation of cell growth, cell differentiation, and a variety of specific cellular responses. A number of medically useful proteins, including erythropoietin, granulocyte-macrophage colony stimulating factor, human growth hormone, and various interleukins, are secreted proteins. Thus, an important goal in the design and development of new therapies is the identification and characterization of secreted and transmembrane proteins and the genes which encode them.

Many secreted proteins are receptors which bind a ligand and transduce an intracellular signal, leading to a variety of cellular responses. The identification and characterization of such a receptor enables one to identify both the ligands which bind to the receptor and the intracellular molecules and signal transduction pathways associated with the receptor, permitting one to identify or design modulators of receptor activity, e.g., receptor agonists or antagonists and modulators of signal transduction.

Summary of the Invention

The present invention is based, at least in part, on the discovery of cDNA molecules encoding TANGO 180, TANGO

181, TANGO 182, TANGO 183, TANGO 184, TANGO 185, TANGO 186, TANGO 187, TANGO 188, TANGO 189, and TANGO 215, all of which are predicted to be either wholly secreted or transmembrane proteins. These proteins, fragments, derivatives, and variants thereof are collectively referred to as "polypeptides of the invention" or "proteins of the invention." Nucleic acid molecules encoding polypeptides of the invention are collectively referred to as "nucleic acids of the invention."

The nucleic acids and polypeptides of the present invention are useful as modulating agents in regulating a variety of cellular processes. Accordingly, in one aspect, the present invention provides isolated nucleic acid molecules encoding a polypeptide of the invention or a biologically active portion thereof. The present invention also provides nucleic acid molecules which are suitable as primers or hybridization probes for the detection of nucleic acids encoding a polypeptide of the invention.

The invention features nucleic acid molecules which are at least 45% (or 55%, 65%, 75%, 85%, 95%, or 98%) identical to the nucleotide sequence of any of SEQ ID Nos:1-22, 34-43 and ___ -___ or the nucleotide sequence of the cDNA of a clone deposited with ATCC as any of Accession Numbers 98899, 98900 and 98901 (the "cDNA of a clone deposited as any of ATCC 98899, 98900, and 989001"), or a complement thereof.

The invention features nucleic acid molecules which include a fragment of at least 300 (325, 350, 375, 400, 425, 450, 500, 550, 600, 650, 700, 800, 900, 1000, or 1200) nucleotides of the nucleotide sequence of any of SEQ ID Nos:1-22, 34-43 and ___ -___ or the nucleotide sequence of the cDNA of a clone deposited as any of ATCC 98899, 98900, and 989001, or a complement thereof.

The invention also features nucleic acid molecules which include a nucleotide sequence encoding a protein having an amino acid sequence that is at least 45% (or 55%, 65%, 75%, 85%, 95%, or 98%) identical to the amino acid sequence of any of SEQ ID Nos:23-33, 54-63, and __ - __ or the amino acid sequence encoded by the cDNA of a clone deposited as any of ATCC 98899, 98900, and 989001, or a complement thereof.

In preferred embodiments, the nucleic acid molecules have the nucleotide sequence of any of SEQ ID NOs:1-22, 34-43 and __ - ___ or the nucleotide sequence of the cDNA of a clone deposited as any of ATCC 98899, 98900, and 989001.

Also within the invention are nucleic acid molecules which encode a fragment of a polypeptide having the amino acid sequence of any of SEQ ID Nos:23-33, 54-63, and ___ - ___ the fragment including at least 15 (25, 30, 50, 100, 150, 300, or 400) contiguous amino acids of any of SEQ ID Nos:23-33, 54-63, and ___ - ___ or the polypeptide encoded by the cDNA of a clone deposited as any of ATCC 98899, 98900, and 989001.

The invention includes nucleic acid molecules which encode a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of any of SEQ ID Nos:23-33, 54-63, and ___ - ___ or an amino acid sequence encoded by the cDNA of a clone deposited as any of ATCC 98899, 98900, and 989001, wherein the nucleic acid molecule hybridizes under stringent conditions to a nucleic acid molecule having a nucleic acid sequence encoding any of SEQ ID NOs:22-33, 54-63, and ___ - ___, or a complement thereof.

Also within the invention are: isolated polypeptides or proteins having an amino acid sequence that is at least about 65%, preferably 75%, 85%, 95%, or 98% identical to

the amino acid sequence of any of SEQ ID NOs: 22-33, 54-63, and ___ - ___.

Also within the invention are: isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence that is at least about 65%, preferably 75%, 85%, or 95% identical the nucleic acid sequence encoding any of SEQ ID Nos:22-33, 54-63, and __ - __ and isolated polypeptides or proteins which are encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule having the sequence of any of SEQ ID NOs:1-22, 34-43, and __ - ___, and a complement thereof or the non-coding strand of the cDNA of a clone deposited as any of ATCC 98899, 98900, and 989001.

Also within the invention are polypeptides which are naturally occurring allelic variants of a polypeptide that includes the amino acid sequence of any of SEQ ID NOs:22-33, 54-63, and __ - ___ or an amino acid sequence encoded by the cDNA of a clone deposited as any of ATCC 98899, 98900, and 989001, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes under stringent conditions to a nucleic acid molecule having the sequence of any of SEQ ID NOs:1-22, 34-43, and __ - ___ or a complement thereof.

The invention also features nucleic acid molecules that hybridize under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence of any of SEQ ID NOs:1-22, 34-43, and __ - ___, of the cDNA of a clone deposited as any of ATCC 98899, 98900, and 989001, or a complement thereof. In other embodiments, the nucleic acid molecules are at least 300 (325, 350, 375, 400, 425, 450, 500, 550, 600, 650, 700, 800, 900, 1000, or 1290) nucleotides in length and hybridize under stringent conditions to a nucleic acid molecule comprising the

nucleotide sequence of any of SEQ ID NOs:1-22, 34-43, and ___ - ___ of the cDNA of a clone deposited as any of ATCC 98899, 98900, and 989001, or a complement thereof. In preferred embodiments, the isolated nucleic acid molecules encode a cytoplasmic, transmembrane, or extracellular domain of a polypeptide of the invention. In another embodiment, the invention provides an isolated nucleic acid molecule which is antisense to the coding strand of a nucleic acid of the invention.

Another aspect of the invention provides vectors, e.g., recombinant expression vectors, comprising a nucleic acid molecule of the invention. In another embodiment the invention provides host cells containing such a vector. The invention also provides methods for producing a polypeptide of the invention by culturing, in a suitable medium, a host cell of the invention containing a recombinant expression vector encoding a polypeptide of the invention such that the polypeptide of the invention is produced.

Another aspect of this invention features isolated or recombinant proteins and polypeptides of the invention. Preferred proteins and polypeptides possess at least one biological activity possessed by the corresponding naturally-occurring human polypeptide. An activity, a biological activity, and a functional activity of a polypeptide of the invention refers to an activity exerted by a protein or polypeptide of the invention on a responsive cell as determined *in vivo*, or *in vitro*, according to standard techniques. Such activities can be a direct activity, such as an association with or an enzymatic activity on a second protein or an indirect activity, such as a cellular signaling activity mediated by interaction of the protein with a second protein. Thus, such activities include, e.g., (1) the ability to form protein-protein interactions with proteins in the

signaling pathway of the naturally-occurring polypeptide; (2) the ability to bind a ligand of the naturally-occurring polypeptide; (3) the ability to bind to an intracellular target of the naturally-occurring polypeptide. Other activities include: (1) the ability to modulate cellular proliferation; (2) the ability to modulate cellular differentiation; and (3) the ability to modulate cell death.

In one embodiment, a polypeptide of the invention has an amino acid sequence sufficiently identical to an identified domain of a polypeptide of the invention. As used herein, the term "sufficiently identical" refers to a first amino acid or nucleotide sequence which contains a sufficient or minimum number of identical or equivalent (e.g., with a similar side chain) amino acid residues or nucleotides to a second amino acid or nucleotide sequence such that the first and second amino acid or nucleotide sequences have a common structural domain and/or common functional activity. For example, amino acid or nucleotide sequences which contain a common structural domain having about 65% identity, preferably 75% identity, more preferably 85%, 95%, or 98% identity are defined herein as sufficiently identical.

In one embodiment, the isolated polypeptide of the invention lacks both a transmembrane and a cytoplasmic domain. In another embodiment, the polypeptide lacks both a transmembrane domain and a cytoplasmic domain and is soluble under physiological conditions.

The polypeptides of the present invention, or biologically active portions thereof, can be operably linked to a heterologous amino acid sequence to form fusion proteins. The invention further features antibodies that specifically bind a polypeptide of the invention such as monoclonal or polyclonal antibodies. In addition, the polypeptides of the invention or

biologically active portions thereof can be incorporated into pharmaceutical compositions, which optionally include pharmaceutically acceptable carriers.

In another aspect, the present invention provides methods for detecting the presence of the activity or expression of a polypeptide of the invention in a biological sample by contacting the biological sample with an agent capable of detecting an indicator of activity such that the presence of activity is detected in the biological sample.

In another aspect, the invention provides methods for modulating activity of a polypeptide of the invention comprising contacting a cell with an agent that modulates (inhibits or stimulates) the activity or expression of a polypeptide of the invention such that activity or expression in the cell is modulated. In one embodiment, the agent is an antibody that specifically binds to a polypeptide of the invention.

In another embodiment, the agent modulates expression of a polypeptide of the invention by modulating transcription, splicing, or translation of an mRNA encoding a polypeptide of the invention. In yet another embodiment, the agent is a nucleic acid molecule having a nucleotide sequence that is antisense to the coding strand of an mRNA encoding a polypeptide of the invention.

The present invention also provides methods to treat a subject having a disorder characterized by aberrant activity of a polypeptide of the invention or aberrant expression of a nucleic acid of the invention by administering an agent which is a modulator of the activity of a polypeptide of the invention or a modulator of the expression of a nucleic acid of the invention to the subject. In one embodiment, the modulator is a protein of the invention. In another embodiment, the

modulator is a nucleic acid of the invention. In other embodiments, the modulator is a peptide, peptidomimetic, or other small molecule.

The present invention also provides diagnostic assays for identifying the presence or absence of a genetic lesion or mutation characterized by at least one of: (i) aberrant modification or mutation of a gene encoding a polypeptide of the invention, (ii) mis-regulation of a gene encoding a polypeptide of the invention, and (iii) aberrant post-translational modification of a polypeptide of the invention wherein a wild-type form of the gene encodes a polypeptide having the activity of the polypeptide of the invention.

In another aspect, the invention provides a method for identifying a compound that binds to or modulates the activity of a polypeptide of the invention. In general, such methods entail measuring a biological activity of the polypeptide in the presence and absence of a test compound and identifying those compounds which alter the activity of the polypeptide.

The invention also features methods for identifying a compound which modulates the expression of a polypeptide or nucleic acid of the invention by measuring the expression of the polypeptide or nucleic acid in the presence and absence of the compound.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

Brief Description of the Drawings

Figure 1 depicts the cDNA sequence (SEQ ID NO:1) and predicted amino acid sequence (SEQ ID NO:23) of human TANGO 180.

Figure 2 depicts the cDNA sequence (SEQ ID NO:34) and predicted amino acid sequence (SEQ ID NO:54) of murine TANGO 180.

Figure 3 depicts the cDNA sequence (SEQ ID NO:2) and predicted amino acid sequence (SEQ ID NO:24) of human TANGO 181.

Figure 4 depicts the partial cDNA sequence (SEQ ID NO:35; partial) and predicted amino acid sequence (SEQ ID NO:55; partial) of murine TANGO 181.

Figure 5 depicts the cDNA sequence (SEQ ID NO:3) and predicted amino acid sequence (SEQ ID NO:25) of human TANGO 182.

Figure 6 depicts the partial cDNA sequence (SEQ ID NO:36; partial) and predicted amino acid sequence (SEQ ID NO:56; partial) of murine TANGO 182.

Figure 7 depicts the cDNA sequence (SEQ ID NO:4) and predicted amino acid sequence (SEQ ID NO:26) of human TANGO 183.

Figure 8 depicts the cDNA sequence (SEQ ID NO:37) and predicted amino acid sequence (SEQ ID NO:57) of murine TANGO 183.

Figure 9 depicts the cDNA sequence (SEQ ID NO:5) and predicted amino acid sequence (SEQ ID NO:27) of human TANGO 184.

Figure 10 depicts the cDNA sequence (SEQ ID NO:38) and predicted amino acid sequence (SEQ ID NO:58) of murine TANGO 184.

Figure 11 depicts the cDNA sequence (SEQ ID NO:6) and predicted amino acid sequence (SEQ ID NO:28) of human TANGO 185.

Figure 12 depicts the cDNA sequence (SEQ ID NO:39) and predicted amino acid sequence (SEQ ID NO:59) of murine TANGO 185.

Figure 13 depicts the cDNA sequence (SEQ ID NO:7) and predicted amino acid sequence (SEQ ID NO:29) of human TANGO 186.

Figure 14 depicts the cDNA sequence (SEQ ID NO:40) and predicted amino acid sequence (SEQ ID NO:60) of murine TANGO 186.

Figure 15 depicts the cDNA sequence (SEQ ID NO:8) and predicted amino acid sequence (SEQ ID NO:30) of human TANGO 188.

Figure 16 depicts the cDNA sequence (SEQ ID NO:41) and predicted amino acid sequence (SEQ ID NO:61) of murine TANGO 188.

Figure 17 depicts the cDNA sequence (SEQ ID NO:9) and predicted amino acid sequence (SEQ ID NO:31) of human TANGO 189.

Figure 18 depicts the cDNA sequence (SEQ ID NO:42) and predicted amino acid sequence (SEQ ID NO:62) of murine TANGO 189.

Figure 19 depicts the cDNA sequence (SEQ ID NO:10) and predicted amino acid sequence (SEQ ID NO:32) of human TANGO 215.

Figure 20 depicts the cDNA sequence (SEQ ID NO:11) and predicted amino sequence of human TANGO 187-1/3 (SEQ ID NO:22).

Figure 21 depicts the cDNA sequence (SEQ ID NO:43; partial) and predicted amino acid sequence of murine TANGO 187 (SEQ ID NO:63; partial).

Figure 22 depicts an alignment of the predicted amino acid sequences of human (SEQ ID NO:23) and murine (SEQ ID NO:54) TANGO 180.

Figure 23 depicts an alignment of the predicted amino acid sequences of human (SEQ ID NO:24) and murine (SEQ ID NO:55; partial) TANGO 181.

Figure 24 depicts an alignment of the predicted amino acid sequences of human (SEQ ID NO:25) and murine (SEQ ID NO:5; partial) TANGO 182.

Figure 25 depicts an alignment of the predicted amino acid sequences of human (SEQ ID NO:26) and murine (SEQ ID NO:57) TANGO 183.

Figure 26 depicts an alignment of the predicted amino acid sequences of human (SEQ ID NO:27) and murine (SEQ ID NO:58) TANGO 184.

Figure 27 depicts an alignment of the predicted amino acid sequences of human (SEQ ID NO:28) and murine (SEQ ID NO:59) TANGO 185.

Figure 28 depicts an alignment of the predicted amino acid sequences of human (SEQ ID NO:29) and murine (SEQ ID NO:60) TANGO 186.

Figure 29 depicts an alignment of the predicted amino acid sequences of human (SEQ ID NO:30) and murine (SEQ ID NO:61) TANGO 188.

Figure 30 depicts an alignment of the predicted amino acid sequences of human (SEQ ID NO:31) and murine (SEQ ID NO:62) TANGO 189.

Figure 31 depicts an alignment of the predicted amino acid sequences of human (SEQ ID NO:33) and murine (SEQ ID NO:63; partial) TANGO 187.

Figure 32 depicts an alignment of the cDNA sequences of human (SEQ ID NO:1) and murine (SEQ ID NO:34) TANGO 180.

Figure 33 depicts an alignment of the cDNA sequences of human (SEQ ID NO:2) and murine (SEQ ID NO:35; partial) TANGO 181.

Figure 34 depicts an alignment of the cDNA sequences of human (SEQ ID NO:3) and murine (SEQ ID NO:36; partial) TANGO 182.

Figure 35 depicts an alignment of the cDNA sequences of human (SEQ ID NO:4) and murine (SEQ ID NO:37) TANGO 183.

Figure 36 depicts an alignment of the cDNA sequences of human (SEQ ID NO:5) and murine (SEQ ID NO:38) TANGO 184.

Figure 37 depicts an alignment of the cDNA sequences of human (SEQ ID NO:6) and murine (SEQ ID NO:39) TANGO 185.

Figure 38 depicts an alignment of the cDNA sequences of human (SEQ ID NO:7) and murine (SEQ ID NO:40) TANGO 186.

Figure 39 depicts an alignment of the cDNA sequences of human (SEQ ID NO:8) and murine (SEQ ID NO:41) TANGO 188.

Figure 40 depicts an alignment of the cDNA sequences of human (SEQ ID NO:9) and murine (SEQ ID NO:42) TANGO 189.

Figure 41 depicts an alignment of the cDNA sequences of human (SEQ ID NO:11) and murine (SEQ ID NO:43; partial) TANGO 187.

Figure 42 depicts an alignment of the amino acid sequences of human TANGO 181 (SEQ ID NO:24), murine TANGO 181 (SEQ ID NO:55; partial), human TANGO 182 (SEQ ID NO:25), and murine TANGO 182 (SEQ ID NO:56; partial).

Figure 43 depicts an alignment of the amino acid sequences of human TANGO 184 (SEQ ID NO:27) and human TANGO 183 (SEQ ID NO:26).

Figure 44 depicts an alignment of the amino acid sequences of murine TANGO 184 (SEQ ID NO:58) and murine TANGO 183 (SEQ ID NO:57).

Figure 45 depicts and alignment of the amino acid sequences of human TANGO 180 (SEQ ID NO:23), murine TANGO 180 (SEQ ID NO:54), agkistrodon PLA2 (SQ ID NO:109), acanthahis PLA2 (SEQ ID NO:110), and bovine PLA2 (SEQ ID NO:111).

Figure 46 depicts the cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of TANGO 187-1.

Figure 47 depicts the cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of TANGO 187-2/3.

Figure 48 depicts the cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of TANGO 187-1/2/3.

Figure 49 depicts the cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of TANGO 187-1/2.

Figure 50 depicts the cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of TANGO 187-2.

Figure 51 depicts the cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of TANGO 187-3.

Figure 52 depicts the cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of TANGO 187.

Figure 53 depicts a complete cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of murine TANGO 181.

Figure 54 depicts a complete cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of murine TANGO 182.

Figure 55 depicts a complete cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of murine TANGO 187.

Figure 56 depicts a complete cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of murine TANGO 215.

Detailed Description of the Invention

The present invention is based on the discovery of cDNA molecules encoding TANGO 180, TANGO 181, TANGO 182, TANGO 183, TANGO 184, TANGO 185, TANGO 186, TANGO 188, TANGO 189, TANGO 215, and TANGO 187, all of which are predicted to be either wholly secreted or transmembrane proteins.

TANGO 180

The human TANGO 180 cDNA of SEQ ID NO:1 has a 567 nucleotide open reading frame (SEQ ID NO:12) encoding a 189 amino acid protein (SEQ ID NO:23). The cDNA and protein sequences of human TANGO 180 are shown in Figure 1.

Human TANGO 180 is predicted to be a wholly secreted protein having a 22 amino acid signal sequence (amino acids 1 - 22 of SEQ ID NO:23; SEQ ID NO:64) followed by a 167 amino acid mature protein (amino acids 23 - 189 of SEQ ID NO:23; SEQ ID NO:76). TANGO 180 is predicted to have a molecular weight of 21.0 kDa prior to cleavage of its signal peptide and a molecular weight of 18.5 kDa subsequent to cleavage of its signal peptide.

The murine TANGO 180 of SEQ ID NO:34 has a 576 nucleotide open reading frame (SEQ ID NO:44) encoding a 192 amino acid protein (SEQ ID NO:54). The cDNA and protein sequences of murine TANGO 180 are shown in Figure 2.

Figure 22 depicts an alignment of the predicted amino acids sequences of human (SEQ ID NO:23) and murine (SEQ ID NO:54) TANGO 180 (88.7% identity). Figure 32 depicts an alignment of the cDNA sequences of human (SEQ ID NO:1) and murine (SEQ ID NO:34) TANGO 180 (55% identity).

Northern analysis of human TANGO 180 mRNA expression revealed the presence of two major transcripts (1.3 and 5.25 kb) and three minor transcripts (0.95, 1.8, and 4.15 kb). This analysis also revealed that all five transcripts are expressed at a low level in placenta, lung, and liver; that the 1.3 and the 5.25 kb transcripts are expressed at a moderate level in brain and kidney; that the 5.25 kb transcript is expressed at a moderate level in heart, skeletal muscle, and pancreas; and that the 1.3 kb transcript is expressed at a high level in heart, skeletal muscle, and pancreas.

In situ expression analysis of TANGO 180 in adult murine tissue revealed no significant expression in bladder, pancreas, heart, thymus, kidney, brain, colon, placenta, eye, liver, spleen, lung, skeletal muscle/diaphram, or small intestine. *In situ* expression analysis of murine embryonic tissue revealed expression in the liver at E13.5 through E16.5. Liver expression was also observed, although at a lower level, at E17.5 and P1.5.

TANGO 180 maps to human chromosome location 4q25.

TANGO 180 is predicted to have a phospholipase A2 histidine active site domain at amino acids 106-113 of SEQ ID NO:23 and a phospholipase A2 aspartic acid active site-like domain at amino acids 124-131 of SEQ ID NO:23.

An apparent genomic sequence of TANGO 180 appears at GenBank Accession Number AC004067.

Human TANGO 180 bears some similarity to a number of *C. elegans* proteins.

TANGO 180 bears some similarity to a number of known phospholipase A2 (PLA2) proteins (Lambeau et al. (1994) *J. Biol. Chem.* 269:1575-78; Lambeau et al. (1995) *J. Biol. Chem.* 270:5534-40). TANGO 180 may play a role similar to that of a phospholipase A2. Figure 45 depicts and alignment of the amino acid sequences of human TANGO 180 (SEQ ID NO:23), murine TANGO 180 (SEQ ID NO:54), agkistrodon PLA2 (SQ ID NO:109), acanthahis PLA2 (SEQ ID NO:110), and bovine PLA2 (SEQ ID NO:111). There are thought to be at least two important regions within many PLA2's: CCXXHCCX (hisitidine at active site) and LIVMACLIVMFYWPCSTCDXXXXXC (aspratic acid active site). Various phospholipase A2 proteins are thought to be involved in inflammation. Moreover, it appears that the expression and synthesis of at least some phospholipase A2 proteins are induced by pro-inflammatory modulators such as interleukin-1, interleukin-6, and tumor necrosis

factor. Thus, TANGO 180 may be involved in inflammation, e.g., arthritis, endotoxic shock, peritonitis, psoriasis, acute pancreatitis, and respiratory distress syndrome. Accordingly, TANGO 180 nucleic acid molecules and polypeptides as well as anti-TANGO 180 antibodies and modulators of TANGO 180 expression or activity may be useful in the treatment of such disorders. Moreover, PLA2's have been implicates in digestion, airway contraction, smooth muslce contraction, fertilization, and cell proliferation. Thus, TANGO 180 nucleic acid molecules and polypeptides as well as anti-TANGO 180 antibodies and modulators of TANGO 180 expression or activity may be useful in the treatment of disorders of digestion, airway contraction, smooth muslce contraction, fertilization, and cell proliferation.

TANGO 181

The human TANGO 181 cDNA of SEQ ID NO:2 has a 1017 nucleotide open reading frame (SEQ ID NO:12) encoding a 339 amino acid protein (SEQ ID NO:23). The cDNA and protein sequences of human TANGO 181 are shown in Figure 3.

Human TANGO 181 is predicted to be a secreted protein having a 22 amino acid signal sequence (amino acids 1 - 22 of SEQ ID NO:24; SEQ ID NO:65) followed by a 317 amino acid mature protein (amino acids 23 - 339 of SEQ ID NO:24; SEQ ID NO:77). TANGO 181 is predicted to have a molecular weight of 37.8 kDa prior to cleavage of its signal peptide and a molecular weight of 35.2 subsequent to cleavage of its signal peptide.

The murine TANGO 181 partial cDNA of SEQ ID NO:35 has a 747 nucleotide open reading frame (SEQ ID NO:45) encoding a 249 amino acid protein (SEQ ID NO:55). The partial cDNA and protein sequences of murine TANGO 181 are shown in Figure 4.

Figure 23 depicts an alignment of the predicted amino acids sequences of human (SEQ ID NO:24) and murine (SEQ ID NO:55; partial) TANGO 181 (72.1% identity). Figure 33 depicts an alignment of the cDNA sequences of human (SEQ ID NO:2) and murine (SEQ ID NO:35; partial) TANGO 181 (65.4% identity). The pair of cysteines at amino acids 76 and 129 might be important for disulfide bond formation. The single cysteine at amino acid 262 might enable TANGO 181 to form homodimers (or heterodimers with TANGO 182).

The cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of a full-length murine TANGO 181 clone are shown in Figure 53.

Northern analysis of human TANGO 181 mRNA expression revealed the presence of two transcripts (4.3 and 4.5 kb) expressed at a low level in heart, brain, placenta, lung, liver, skeletal muscle, kidney, and pancreas, with the level of expression in the pancreas being higher than in the other tissues.

Murine *in situ* expression analysis revealed that TANGO 181 is weakly expressed in adult brain (choroid plexus and olfactory bulb). This analysis also revealed TANGO 180 expression in the liver and kidney (medulla). High level TANGO 180 expression was observed in testis. This analysis detected little or no expression of TANGO 181 in adult liver, ovary, heart, lung, spleen, fat, muscle, skin, stomach, duodenum, colon, pancreas, thymus, pituitary, and eye. *In situ* expression analysis of embryos revealed that TANGO 181 is ubiquitously expressed at stages E12.5, E13.5, and E14.5.

TANGO 181 maps to human chromosome location 8p12. WI-5768 and AFMB057WG5 are markers which flank TANGO 181. Nearby loci include WRN (Werner Syndrome) and SPG5A (Spastic Paraplegia 5A), and nearby known genes include FGFR1 (fibroblast growth factor receptor), STAR

(Steroidogenic acute regulatory protein), ANK1 (abkyrin 1), CALB1 (calbindin 1), CHRNB3 (cholinergic receptor, nicotinic). The human chromosomal location corresponds to a position on mouse chromosome 8 near fgfri (fibroblast growth factor receptor), cyrn (cyritesin 1), tissue plasminogen activator, and ank (ankyrin 1).

Within the 3' untranslated region of the human TANGO 181 cDNA described above is a 260 base pair sequence (Genbank Accession Number Z36802) previously identified as part of a gene that appears to be preferentially expressed in pancreatic cancer and chronic pancreatitis (Gress et al. (1996) *Oncogene* 13:1819-30). Thus, TANGO 181 nucleic acids and polypeptides may be useful for the diagnosis and/or treatment of chronic pancreatitis and pancreatic cancer (as well as other cancers). In addition, modulators of TANGO 181 expression or activity may be useful in the treatment of such disorders.

TANGO 181 and TANGO 182 are highly homologous to teh C. elegans protein C42C1.9

TANGO 182

The human TANGO 182 cDNA of SEQ ID NO:3 has a 1044 nucleotide open reading frame (SEQ ID NO:14) encoding a 348 amino acid protein (SEQ ID NO:25). The cDNA and protein sequences of human TANGO 182 are shown in Figure 5.

Human TANGO 182 is predicted to be a secreted protein having a 23 amino acid signal sequence (amino acids 1 - 23 of SEQ ID NO:25; SEQ ID NO:66) followed by a 325 amino acid mature protein (amino acids 24 - 348 of SEQ ID NO:25; SEQ ID NO:78). TANGO 182 is predicted to have a molecular weight of 39.2 kDa prior to cleavage of its signal peptide and a molecular weight of 36.1 kDa subsequent to cleavage of its signal peptide.

The murine TANGO 182 partial cDNA of SEQ ID NO:36 has an 825 nucleotide open reading frame (SEQ ID NO:46) encoding a 275 amino acid protein (SEQ ID NO:56). The partial cDNA and protein sequences of murine TANGO 182 are shown in Figure 6. Figure 24 depicts an alignment of the predicted amino acids sequences of human (SEQ ID NO:25) and murine (SEQ ID NO:56; partial) TANGO 182 (75.1% identity). Figure 34 depicts an alignment of the cDNA sequences of human (SEQ ID NO:3) and murine (SEQ ID NO:36; partial) TANGO 182 (67.6% identity). The pair of cysteines at amino acids 78 and 130 might be important for disulfide bond formation. The single cysteine at amino acid 312 might enable TANGO 182 to form homodimers (or heterodimers with TANGO 181).

The cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of a full-length murine TANGO 182 clone are shown in Figure 54.

TANGO 182 maps to human chromosomal location 10q24 between markers D10S566 and D10S540. In mice, TANGO 182 maps to chromosome 10 bwtween D10S198 and D10S192 (129.8 to 131.2 cM).

Northern analysis of human TANGO 182 mRNA expression revealed the presence of a 2.8 kb transcript that is expressed at a high level placenta and a somewhat lower level in liver, kidney, and pancreas. This transcript is expressed at a low level in heart, brain, lung, and skeletal muscle.

Murine *in situ* expression analysis revealed that TANGO 182 is expressed at a high level in testis in adult mice. Little or no expression was detected in adult brain, liver, kidney, ovary, heart, lung, spleen, fat, muscle, skin, stomach, duodenum, colon, pancreas, thymus, pituitary, or eye by *in situ* analysis. *In situ*

expression analysis of embryos revealed ubiquitous, low level expression at stages E12.5, E13.5, and E14.5.

Both human and mouse TANGO 182 are quite similar to human and murine TANGO 181 at the amino acid level (Figure 42). Thus, TANGO 182, like TANGO 181, may be useful for the diagnosis and/or treatment of pancreatic cancer and chronic pancreatitis as well as other cancers. In addition, TANGO 182 bears some similarity to a *C. elegans* protein C42C1.9 (Genbank Accession Number AF043695) that is encoded by a gene that is present in the same operon as a gene encoding a mitochondrial carrier protein. Since genes within the same operon are often co-regulated and encode proteins involved in the same physiological state, TANGO 182 may play a role in metabolism. Thus, TANGO 182 nucleic acids and polypeptides as well as antibodies directed against TANGO 182 may be useful in the diagnosis and treatment of metabolic disorders. In addition, modulators of TANGO 182 expression or activity may be useful in the treatment of such disorders.

TANGO 183

The human TANGO 183 cDNA of SEQ ID NO:4 has a 549 nucleotide open reading frame (SEQ ID NO:15) encoding a 183 amino acid protein (SEQ ID NO:26). The cDNA and protein sequences of human TANGO 183 are shown in Figure 7.

Human TANGO 183 is predicted to be a transmembrane protein having a 20 amino acid signal sequence (amino acids 1 - 20 of SEQ ID NO:26; SEQ ID NO:67) followed by a 163 amino acid mature protein (amino acids 21 - 183 of SEQ ID NO:26; SEQ ID NO:79) having a 69 amino acid extracellular domain (amino acids 21 - 89 of SEQ ID NO:26; SEQ ID NO:88), a 23 amino acid transmembrane domain (amino acids 90 - 112 of SEQ ID NO:26; SEQ ID

NO:94), and a 71 amino acid cytoplasmic domain (amino acids 113 - 183 of SEQ ID NO 26; SEQ ID NO: 102). There are 8 conserved cysteines in the extracellular domain. TANGO 183 has a high porportion of charged amino acids in the predicted extracellular (18%, not including histidines) and cytoplasmic (32%) domains. Human TANGO 183 is predicted to have a molecular weight of 20.6 kDa prior to cleavage of its signal peptide and a molecular weight of 18.1 kDa subsequent to cleavage of its signal peptide.

The murine TANGO 183 cDNA of SEQ ID NO:37 has a 549 nucleotide open reading frame (SEQ ID NO:47) encoding a 183 amino acid protein (SEQ ID NO:57). The cDNA and protein sequences of murine TANGO 183 are shown in Figure 8.

Figure 25 depicts an alignment of the predicted amino acids sequences of human (SEQ ID NO:26) and murine (SEQ ID NO:57) TANGO 183 (97.3% identity). Figure 35 depicts an alignment of the cDNA sequences of human (SEQ ID NO:4) and murine (SEQ ID NO:37) TANGO 183 (71.7% identity). The conserved cysteine residues are particularly important and are preferably retained in functional variants.

Northern analysis of human TANGO 183 mRNA expression revealed the presence of a 1.6 kb transcript that is expressed at a high level in brain, kidney, pancreas, and heart; at a moderate level in liver and skeletal muscle, and at a low level in placenta and lung.

The nucleic acid sequence of TANGO 183 is related to a sequence tagged site at chromosomal location 11p15.4, and TANGO may map to this site.

The predicted cytoplasmic domain of TANGO 183 has a relatively high number of charged residues (32%). This suggests that TANGO 183 may non-covalently, e.g., electrostatically, associate with an intracellular

molecule such as a cytoskeletal component. Accordingly, TANGO 183 may itself be involved in maintaining the structural integrity of cells in which it is expressed. If so, aberrant TANGO 183 protein or aberrantly regulated TANGO 183 could be involved in alterations in cellular morphology, e.g., alterations associated with metastasis. Accordingly, TANGO 183 nucleic acid molecules and polypeptides as well as anti-TANGO 183 antibodies and modulators of TANGO 183 expression or activity may be useful in the treatment of disorders associated with aberrant cell development or cell differentiation, e.g., cancer, or cell migration, e.g., tumor metastasis.

TANGO 183 and TANGO 184 are related and may play similar functional roles. Figure 43 depicts an alignment of the amino acid sequences of human TANGO 184 (SEQ ID NO:27) and human TANGO 183 (SEQ ID NO:26). Figure 44 depicts an alignment of the amino acid sequences of murine TANGO 184 (SEQ ID NO:58) and murine TANGO 183 (SEQ ID NO:57).

TANGO 183 is related to *C. elegans* R12C12.6 (GenBank Accession NO. U23510).

TANGO 184

The human TANGO 184 cDNA of SEQ ID NO:5 has a 594 nucleotide open reading frame (SEQ ID NO:16) encoding a 198 amino acid protein (SEQ ID NO:27). The cDNA and protein sequences of human TANGO 184 are shown in Figure 9.

Human TANGO 184 is predicted to be a transmembrane protein having a 28 amino acid signal sequence (amino acids 1 - 28 of SEQ ID NO:27; SEQ ID NO:68) followed by a 170 amino acid mature protein (amino acids 29 - 198 of SEQ ID NO:27; SEQ ID NO:80) having a 74 amino acid extracellular domain (amino acids 29 - 102 of SEQ ID NO: 27; SEQ ID NO:89), a 23 amino acid transmembrane domain

(amino acids 103 - 125 of SEQ ID NO:27; SEQ ID NO:95), and a 73 amino acid cytoplasmic domain (amino acids 126 - 198 of SEQ ID NO 27; SEQ ID NO:103). TANGO 184 has a high porportion of charged amino acids in the predicted extracellular (31%) and cytoplasmic (29%) domains. Notably, the transmembrane regions include charged residues. Human TANGO 184 is predicted to have a molecular weight of 22.5 kDa prior to cleavage of its signal peptide and a molecular weight of 18.9 kDa subsequent to cleavage of its signal peptide.

The murine TANGO 184 cDNA of SEQ ID NO:38 has a 357 nucleotide open reading frame (SEQ ID NO:48) encoding a 199 amino acid protein (SEQ ID NO:58). The cDNA and protein sequences of murine TANGO 184 are shown in Figure 10.

Figure 26 depicts an alignment of the predicted amino acids sequences of human (SEQ ID NO:27) and murine (SEQ ID NO:58) TANGO 184 (94.5% identity). Figure 36 depicts an alignment of the cDNA sequences of human (SEQ ID NO:5) and murine (SEQ ID NO:38) TANGO 184 (63.8% identity).

Northern analysis of human TANGO 184 mRNA expression revealed the presence of a 2 kb transcript that is expressed at a high level in heart brain, placenta, skeletal muscle, kidney, and pancreas; and at a low level in lung and liver. There are two alternative polyA sites: nucleotide 1000 and nucleotide 2000.

In situ analysis of TANGO 184 expression in adult mice revel expression in the brain (moderate, ubiquitous expression), spinal cord (weak expression in the region of the grey matter) submandibular gland (strong, ubiquitous expression), stomach (weak expression in the muscle region), Kidney (weak, ubiquitous expression in the cortex and medulla, stronger expression in papilla), adrenal gland (weak ubiquitous expression), thymus (weak expression in cortex), lymph node (moderate ubiquitous

expression) spleen (weak expression in follicles), skeletal muscle/smooth muscle (diaphragm), testis (strong expression in the area surrounding the seminiferous tubules), ovaries (weak expression) placenta (moderate, ubiquitous expression). This analysis did not reveal significant expression in white fat, brown fat, heart, lung, liver, pancreas, colon, small intestine, and bladder. In embryonic tissue, this analysis revealed expression at E13.5 (weak to moderate ubiquitous expression with higher expression in the brain and liver), E14.5 (weak to moderate ubiquitous expression with higher expression in the brain and liver), E15.5 (moderate ubiquitous expression with higer expression in the brain), E16.5 (weak to moderate ubiquitous expression with higher expression in the brain, spinal cord, brown fat, submandibular gland, lung, stomach, and intestines), E18.5 (weak to moderate ubiquitous expression with higher expression in the brain, spinal cord, brown fat, submandibular gland, lung, stomach, and intestines), and P1.5 (weak ubiquitous expression with higer expression in brain, submandibular gland, olfactory epithelium, and stomach).

The predicted cytoplasmic domain of TANGO 184 has a relatively high number of charged residues (29%). This suggests that TANGO 184 may non-covalently, e.g., electrostatically, associate with an intracellular molecule such as a cytoskeletal component. Accordingly, TANGO 184 may itself be involved in maintaining the structural integrity of cells in which it is expressed. If so, aberrant TANGO 184 protein or aberrantly regulated TANGO 184 could be involved in alterations in cellular morphology, e.g., alterations associated with metastasis. Accordingly, TANGO 184 nucleic acid molecules and polypeptides as well as anti-TANGO 184 antibodies and modulators of TANGO 184 expression or activity may be

useful in the treatment of disorders associated with aberrant cell development or cell differentiation, e.g., cancer, or cell migration, e.g., tumor metastasis.

TANGO 185

The human TANGO 185 cDNA of SEQ ID NO:6 has a 579 nucleotide open reading frame (SEQ ID NO:17) encoding a 193 amino acid protein (SEQ ID NO:28). The cDNA and protein sequences of human TANGO 185 are shown in Figure 11.

Human TANGO 185 is predicted to be a transmembrane protein having a 24 amino acid signal sequence (amino acids 1 - 24 of SEQ ID NO:28; SEQ ID NO:69) followed by a 169 amino acid mature protein (amino acids 25 - 193 of SEQ ID NO:28; SEQ ID NO:81) having two extracellular domains, one having 51 amino acids (amino acids 25 - 75 of SEQ ID NO:28; SEQ ID NO:90), and a second having 19 amino acids (amino acids 132 - 150 of SEQ ID NO:28; SEQ ID NO:91); three transmembrane domains, one having 27 amino acids (amino acids 76 - 102 of SEQ ID NO:28; SEQ ID NO:96), a second having 22 amino acids (amino acids 110-131 of SEQ ID NO:28; SEQ ID NO:97), the third having 24 amino acids (amino acids 151 - 174 of SEQ ID NO:28; SEQ ID NO:98); and two cytoplasmic domains, one having 7 amino acids (amino acids 103 - 109 of SEQ ID NO:28; SEQ ID NO:104), and a second having 19 amino acids (amino acids 175 - 193 of SEQ ID NO:28; SEQ ID NO:105). The predicted 22 amino acid transmembrane domain and the predicted 24 amino acid domain, along with the predicted 7 amino acid cytoplasmic domain may form one hydrophobic domain that passes through the membrane twice. TANGO 185 is predicted to have a molecular weight of 21.4 kDa prior to cleavage of its signal peptide and a molecular weight of 18.8 kDa subsequent to cleavage of its signal peptide. Notably, the transmembrane regions have charged residues.

The murine TANGO 185 cDNA of SEQ ID NO:39 has a 579 nucleotide open reading frame (SEQ ID NO:49) encoding a 193 amino acid protein (SEQ ID NO:59). The cDNA and protein sequences of murine TANGO 185 are shown in Figure 12.

Figure 27 depicts an alignment of the predicted amino acids sequences of human (SEQ ID NO:28) and murine (SEQ ID NO:59) TANGO 185 (90.7% identity). Figure 37 depicts an alignment of the cDNA sequences of human (SEQ ID NO:6) and murine (SEQ ID NO:39) TANGO 185 (71.1% identity).

Human TANGO 185 maps to chromosome 6.

Northern analysis of human TANGO 185 mRNA expression revealed the presence of 2.2 kb major transcript and a 4.2 kb minor transcript. This analysis also revealed that the 2.3 kb transcript is expressed at a high level in heart, placenta, and pancreas; at a moderate level in lung, liver, and kidney; and at a very low level, if at all, in brain and skeletal muscle. The 4.2 kb transcript is expressed at a low level in placenta.

In situ analysis of TANGO 185 expression in adult mice revealed expression in the brain (choroid plexus), submamandibular gland (ubiquitous expression), white fat (weak expression, possible mammary gland expression), stomach (mucosal epithelium), kidney (medulla-cortex transition and medullary rays), colon (weak expression in the epithelium), small intestine (villi), thymus (low level expression), bladder (mucosal epithelium), and placenta (ubiquitous expresion in decidua region). This analysis did not reveal significant expression in adult eye and harderian gland, brown fat, heart, lung, liver, spleen, pancreas, skeletal muscle, testes, and ovaries.

In situ analysis of TANGO 185 embryonic expression in mice revealed expression at E13.5 (high level expression the skin and submaxillary gland and low level ubiquitous expression in the liver); E14.5 (high level expression in

the choroid plexus of the lateral and fourth ventricles, skin, epithelium of the oral cavity, follicles of vibrissa, submaxillary gland, stomach, and heart; expression in lung (especially the developing large airways) and liver (ubiquitous expression)). At E15.5 the observed expression pattern is nearly identical to that at E14.5 except that there is expression in the region outlining the intestinal tract and lung expression is ubiguitous with higher expression in the region outlining the large airways.

At E16.5 high level expression is observed in skin choroid plexus, the lining of the oral and nasal cavity, esophagus, bladder, stomach, intestine, large vessels of the heart, large airways of the lung, and the region outlining the vertebrae. Lower ubiquitous expression is present in the heart, lung and thymus. A somewhat higher, multifocal expression is present in the thymus.

At E18.5 the expression pattern is identical to that observed at E16.5 except that expression is also observed in developing hair follicles.

At P1.5 the expression pattern is identical to that observed at E16.5 except that there is no long significant expression in the region outlining the vertebrae.

The expression pattern of TANGO 185 during eubryonic development suggests that TANGO 185 expression is strongly associated with squamous and mucosal epithelial cells.

The expression pattern of TANGO 185 suggests that it is involved in cell development and/or cell differentiation. Accordingly, TANGO 185 nucleic acid molecules and polypeptides as well as anti-TANGO 185 antibodies and modulators of TANGO 185 expression or activity may be useful in the treatment of disorders associated with aberrant cell development or cell differentiation, e.g.,

cancer. There is evidence that TANGO 185 is expressed in prostate cells. Thus, TANGO 185 nucleic acid molecules and polypeptides as well as anti-TANGO 185 antibodies and modulators of TANGO 185 expression or activity may be useful in the treatment of prostate cancer.

TANGO 186

The human TANGO 186 cDNA of SEQ ID NO:7 has a 1149 nucleotide open reading frame (SEQ ID NO:18) encoding a 383 amino acid protein (SEQ ID NO:29). The cDNA and protein sequences of human TANGO 186 are shown in Figure 13.

Human TANGO 186 is predicted to be a secreted protein having a 20 amino acid signal sequence (amino acids 1 - 20 of SEQ ID NO:29; SEQ ID NO:70) followed by a 363 amino acid mature protein (amino acids 21 - 383 of SEQ ID NO:29; SEQ ID NO:82). There are eight cysteines in mature TANGO 186. Some or all of these might be involved in disulfide bond formation. Human TANGO 186 is predicted to have a molecular weight of 43.0 kDa prior to cleavage of its signal peptide and a molecular weight of 40.3 kDa subsequent to cleavage of its signal peptide.

The murine TANGO 186 cDNA of SEQ ID NO:40 has a 1146 nucleotide open reading frame (SEQ ID NO:50) encoding a 382 amino acid protein (SEQ ID NO:60). The cDNA and protein sequences of murine TANGO 186 are shown in Figure 14. Conserved cysteine residues are particularly important and are preferably retained in functional variants

Figure 28 depicts an alignment of the predicted amino acids sequences of human (SEQ ID NO:29) and murine (SEQ ID NO:60) TANGO 186 (90.9% identity). Figure 38 depicts an alignment of the cDNA sequences of human (SEQ ID NO:7) and murine (SEQ ID NO:40) TANGO 186 (41.6% identity). The human and murine TANGO 186 proteins are highly

similar except within three portions: the signal sequence, a hinge region at amino acids 108-123, and a hinge region at amino acids 198-216. Within these three portions the proteins are only about 50% identical. Outside of these three portions the proteins are about 97.3% identical.

TANGO 186 maps to human chromosome 11q14.

Northern analysis of human TANGO 186 mRNA expression revealed the presence of a 1.8 kb transcript and a 4 kb transcript. Both transcripts are expressed at a low level in heart, lung, liver, skeletal muscle, kidney, and pancreas and at a very low level in brain.

In situ analysis of TANGO 186 in adult mice revealed that TANGO 186 is expressed in brain (olfactory bulb), spleen (low level ubiquitous signal), small intestine (very strong signal in villi and submucosa), colon (ubiquitous signal), kidney (cortical and medullary region), lung (bronchial epithelium), eye (iris and cornea), placenta (strong signal in the outer membrane). This analysis did not detect expression in adult pancreas, heart, skeletal muscle, diaphragm, esophagus, liver, and thymus.

In situ expression analysis of murine embryonic sagittal sections revealed expression at stage E13.5 in epithelium of the lower and upper lip, cartilage primordium of basisphenoid bone, cartilage condensation of sacral vertebral body (centrum), small intestine, and heart. At stage E14.5, in addition to the expression observed at stage E13.5, expression was also observed in: eye (or cartilage around eye), Meckel's cartilage, and cartilage of the limb digits. At stage E15.5 expression was observed in vibrissae of the snout, kidney (embryonic glomeruli), cartilage of the limb digits, cartilage of the vertebral column, heart, eye, and small intestine. At stage E16.5 the observed expression pattern was

similar to that observed at E15.5, but there was a notable reduction in signal from cartilage, epithelium of upper and lower lip, and heart. Also at stage E16.5 low level signal was observed in the lung, and a strong signal was still observed in the small intestine. At stage E17.5 expression of TANGO 186 was observed to be more ubiquitous. However, expression in cartilage was observed to decrease with the exception of ossification within cartilage primordium of body of mandible. At stage E17.5 strong expression continued to be observed in the small intestine. The expression pattern at stage P1.5 was observed to be very similar to that observed at stage E17.5 with expression being nearly ubiquitous with the notable exceptions of the brain and spinal cord in which little or no expression was observed. At stage P1.5 the highest expression observed was in the in the small intestine, lung, and kidney.

Overall, the *in situ* expression analysis of adult and embryonic tissue revealed that expression is first observed in the developing cartilage, small intestine, and heart with the cartilage expression being most striking in the developing vertebral column and jaw area. Strong expression in the cartilage of the vertebral column and developing digits was observed through stage E16.5. Subsequently, cartilage expression was observed to decrease with some exceptions in the jaw area. Other embryonic tissue in which the observed expression was notable include the kidney, specifically the embryonic glomeruli, and the lung. These tissues continue to have strong expression in the adult with expression in the kidney also being observed in the medullary region and lung expression becoming restricted to the bronchial epithelium. Expression of TANGO 186 becomes more ubiquitous through P1.5 with the most noticeable

exception being the brain and spinal cord. In the adult, however, signal is observed in the olfactory bulb.

In a murine LPS disease model, increasaed TANGO 186 expression was observed in the brain 2 and 8 hours after LPS treatment. Decrease TANGO 186 expression was observed at these same time points in the kidney. TANGO 186 expression was also observed in the gastric mucosa.

As discussed above, murine *in situ* expression analysis demonstrates that TANGO 186 is expressed in cartilage throughout the embryo, suggesting that TANGO 186 is a regulatory molecule that plays a role in a bone formation (e.g., condensation of cartilage). Accordingly, TANGO 186 nucleic acid molecules and polypeptides as well as anti-TANGO 186 antibodies and modulators of TANGO 186 expression or activity may be useful in the diagnosis and treatment of bone and cartilage disorders (e.g., osteogenesis imperfecta and broken bones, cartilage degradation, and bone degradation). Moreover, many bone morphogenic proteins and TGF-β family members are regulated by extracellular proteins, e.g., noggin and chordin. Thus, TANGO 186, which is expressed in the heart, may play a role in heart development, and TANGO 186 nucleic acid molecules and polypeptides as well as anti-TANGO 186 antibodies and modulators of TANGO 186 expression or activity may be useful in the diagnosis and treatment of developmental disorders of the heart, e.g., valve malformation.

There is some seqeunce similarity between TANGO 186 and a *Bacillus* serine protease. Thus, TANGO 186 may have serine protease activity.

TANGO 188

The human TANGO 188 cDNA of SEQ ID NO:8 has a 792 nucleotide open reading frame (SEQ ID NO:19) encoding a 264 amino acid protein (SEQ ID NO:30). The cDNA and

protein sequences of human TANGO 188 are shown in Figure 15.

Human TANGO 188 is predicted to be a secreted protein having a 23 amino acid signal sequence (amino acids 1 - 23 of SEQ ID NO:30; SEQ ID NO:71) followed by a 241 amino acid mature protein (amino acids 24 - 264 of SEQ ID NO:30; SEQ ID NO:83). Human TANGO 188 is predicted to have a molecular weight of 29.5 kDa, prior to cleavage of its signal peptide.

The murine TANGO 188 cDNA of SEQ ID NO:41 has an 807 nucleotide open reading frame (SEQ ID NO:51) encoding a 269 amino acid protein (SEQ ID NO:61). The cDNA and protein sequences of murine TANGO 188 are shown in Figure 16.

Figure 29 depicts an alignment of the predicted amino acids sequences of human (SEQ ID NO:30) and murine (SEQ ID NO:61) TANGO 188 (80.5% identity). Figure 39 depicts an alignment of the cDNA sequences of human (SEQ ID NO:8) and murine (SEQ ID NO:41) TANGO 188 (71.8% identity).

TANGO 188 maps to human chromosome 16p13.3.

Northern analysis of human TANGO 188 mRNA expression revealed the presence of 2.0 kB transcript that is expressed at a low level in heart and pancreas and at a very low level, if at all, in brain, placenta, lung, liver, skeletal muscle, and kidney.

In situ analysis of TANGO 188 expression in adult mice did not detect significant expression in in the bladder, placenta, pancreas, eye, heart, liver, thymus, spleen, kidney, lung, brain, skeletal muscle/diaphragm, colon, or small intestine. *In situ* analysis of TANGO 188 expression in embryos revealed no significant expression at 13.5, E14.5, E15.5, E16.5, E17.5, or P1.5. However, in the case of both adult mice and embryos, expression of TANGO 188 may have been obscured by a high background signal.

TANGO 188 is transcribed in an anti-sense relationship to NY-CO-7 (Scanlon et al. (1998) *Int. J. Cancer* 76:652-58). Accordingly, TANGO 188 may have utility as a marker for colon cancer, and TANGO 188 nucleic acid molecules and polypeptides as well as anti-TANGO 188 antibodies and modulators of TANGO 188 expression or activity may be useful in the diagnosis and treatment of colon cancer or other types of cancer.

The gene encoding the *C. elegans* homologue of NY-CO-7 is present in the same operon as a gene encoding a mitochondrial import protein. Since genes within the same operon are often co-regulated and encode proteins involved in the same physiological state, TANGO 188 may be a mitochondrial import protein or may be involved in some other mitochondrial function. Thus, TANGO 188 nucleic acids and polypeptides as well as antibodies directed against TANGO 188 and modulators of TANGO 188 expression or activity may be useful in the diagnosis and treatment of disorders associated with defects in mitochondrial function.

TANGO 188 appears to be the homologue of a *C. elegans* protein that is present in the same operon as a gene encoding a protein that bears some similarity to SnF8p, a yeast zinc finger protein that is likely a transcription factor involved in expression of genes encoding certain proteins involved in respiration and metabolism. Since genes within the same operon are often co-regulated and encode proteins involved in the same physiological state, TANGO 188 may play a role in respiration or metabolism. Thus, TANGO 188 nucleic acids and polypeptides as well as antibodies directed against TANGO 188 and modulators of TANGO 188 expression or activity may be useful in the diagnosis and treatment of disorders associated with defects in cell respiration or metabolism.

TANGO 189

The human TANGO 189 cDNA of SEQ ID NO:9 has a 759 nucleotide open reading frame (SEQ ID NO:20) encoding a 253 amino acid protein (SEQ ID NO:31). The cDNA and protein sequences of human TANGO 189 are shown in Figure 17.

The human TANGO 189 cDNA described above (SEQ ID NO:9; Figure 17) represents one splice variant of TANGO 189 (splice variant 1A). There exists a second splice variant of human TANGO 189 (splice variant 1B). The cDNA sequence of this splice variant is the same the cDNA sequence of human TANGO 189 described above, except that nucleotides 674-1087 are missing. This splice variant cDNA encodes a 184 amino acid protein having a predicted molecular weight of 21.1 kDa prior to cleavage of the predicted signal sequence. Both splice variant 1A and splice variant 1B appear to arise from a 2.1 kB transcript which is 2055 nucleotides long, not including the polyA sequence. This transcript encodes a 253 amino acid protein having a predicted molecular weight of 28.6 kDa, not including the predicted signal sequence.

The 2.1 kb TANGO 189 transcript encodes a human TANGO 189 protein that is predicted to be a transmembrane protein having a 24 or 25 amino acid signal sequence (amino acids 1- 24 or 1-25 of SEQ ID NO:31; SEQ ID NO:72 and SEQ ID NO:73) followed by a 227 or 226 amino acid mature protein (amino acids 25 - 251 or 26 - 251 of SEQ ID NO:31; SEQ ID NO:84 and SEQ ID NO:85) having a first extracellular domain of 114 or 115 amino acids (amino acids 25 - 138 or 26 - 138 of SEQ ID NO:31; SEQ ID NO:92 and SEQ ID NO:93), followed by a first transmembrane domain (amino acids 139 - 164 of SEQ ID NO:31; SEQ ID NO:99), a first cytoplasmic domain (amino acids 165 - 177 of SEQ ID NO:31; SEQ ID NO:106), a second transmembrane domain (amino acids 178 - 195 of SEQ ID NO:31; SEQ ID

NO:100), a second extracellular domain (amino acids 196 - 211 of SEQ ID NO:31; SEQ ID NO:108), a third transmembrane domain (amino acids 212 - 237 of SEQ ID NO:31; SEQ ID NO:101), and a second cytoplasmic domain (amino acids 238 - 253 of SEQ ID NO:31; SEQ ID NO:107). The protein encoded by this 2.1 kb TANGO 189 transcript is predicted to have a molecular weight of 21.8 kDa prior to cleavage of its signal peptide and a molecular weight of 25.2 kDa subsequent to cleavage of its signal peptide. The predicted domain structure of the protein encoded splice variant 1A is identical to that of the protein encoded by the 2.1 kb transcript up to amino acid 181. The predicted domain structure of the protein encoded splice variant 1B is identical to that of the protein encoded by the 2.1 kb transcript up to amino acid 180.

The murine TANGO 189 cDNA of SEQ ID NO:42 has a 759 nucleotide open reading frame (SEQ ID NO:52) encoding a 253 amino acid protein (SEQ ID NO:62). The cDNA and protein sequences of murine TANGO 189 are shown in Figure 18.

Figure 30 depicts an alignment of the predicted amino acids sequences of human (SEQ ID NO:31; splice variant 1A) and murine (SEQ ID NO:62) TANGO 189 (91.7% idenity). Figure 40 depicts an alignment of the cDNA sequences of human (SEQ ID NO:9; splice variant 1A) and murine (SEQ ID NO:42) TANGO 189 (51.8% identity).

Northern analysis of human TANGO 189 mRNA expression revealed the presence of one major transcript (2.1 kb) and four minor transcripts (3.4. kb, 4.2 kb, 6 kb, and 7 kb). The 2.1 kB transcript is expressed at a high level in brain, spinal cord, and testis; expressed at a low level in heart, placenta, skeletal muscle, kidney, pancreas, lung, thyroid, lymph node, trachea, adrenal, bone marrow, spleen, ovary, and prostate; and expressed at a very low level in liver, stomach, thymus, small

intestine, colon, peripheral blood lymphocytes. The 3.4. kb, 4.2 kb, 6 kb, and 7 kb transcripts are expressed at a moderate level in brain and spinal cord; and are not expressed in testis. The 4.6 and 7 kb transcripts are expressed at a moderate level in peripheral blood lymphocytes.

Murine *in situ* expression analysis revealed that TANGO 189 is expressed strongly and almost ubiquitously expressed in the mouse embryo. Tissues with the highest expreession during embryogenesis are the brain, spinal chord, and small intestine. Expression decreases in most if not all tissues by postnatal day 1.5 but tissues of highest expression remain the brain, spinal chord, and small intestine. This pattern continues into the adult mouse with expression in most tissues decreasing even more, some to background levels. Of the adult tissue tested, the brain, spleen, small intestine, and retina, have the highest signal. High level expression is observed in the folowing adult tissues: placenta (ubiquitous), small intestine (except villi), eye (retina), brain (ubiquitous). Lower expression is observed in: bladder (stronger signal in the transitional epithelium), kidney, thymus, liver, placenta, spleen, and colon. Expression was not observed in: heart, skeletal muscle, diaphragm, lung, and pancreas. Embryonic expresion was observed at stages E13.5 through E17.5 (high ubiquitous signal, brain, spinal chord, small intestine have the strongest signal) and P1.5 (ubiquitous signal decreased in intensity, brain, spinal chord, small intestine, and kidney have the strongest signal).

TANGO 189 is useful as a tissue-specific marker. The expression of TANGO 189 may be altered in a variety of disease states (e.g., cancer). Thus, TANGO 189 nucleic acid molecules and polypeptides as well as anti-TANGO 189

antibodies and modulators of TANGO 189 disorders cell proliferation and differentiation.

TANGO 215

The human TANGO 215 cDNA of SEQ ID NO:10 has a 2160 nucleotide open reading frame (SEQ ID NO:21) encoding a 720 amino acid protein (SEQ ID NO:32). The cDNA and protein sequences of human TANGO 215 are shown in Figure 19.

The cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of a full-length murine TANGO 181 clone are shown in Figure 56.

Human TANGO 215 is predicted to be a wholly secreted protein having a 21 amino acid signal sequence (amino acids 1 - 21 of SEQ ID NO:32; SEQ ID NO:74) followed by a 699 amino acid mature protein (amino acids 22 - 720 of SEQ ID NO:32; SEQ ID NO:86). TANGO 215 is predicted to have a molecular weight of 80.3 kDa prior to cleavage of its signal peptide and a molecular weight of 77.6 kDa subsequent to cleavage of its signal peptide.

TANGO 215 is related to C1r/C1s (C1q) and MASP1/MASP2 (mannose-binding lectin-associated serine protease) proteases, all of which are involved in the alternative pathway pathway of immune response.

TANGO 215 may be a theronine protease. There is a threonine in the sequence TGG at amino acid 664-666 of human and murine TANGO 215. This sequence is within a region having similarity to the active site of certain proteases. Human TANGO 215 is predicted to have CUB domain (amino acids 128 - 236 of SEQ ID NO:32), an EGF domain (amino acids 239 - 271 of SEQ ID NO:32), a small consensus repeat (SCR) domain (amino acids 280 - 342 of SEQ ID NO:32), a partial SCR domain (amino acids 408 -

442 of SEQ ID NO:32), and a serine protease domain (amino acids 461 - 720 of SEQ ID NO:32).

Northern analysis of human TANGO 215 mRNA expression revealed the presence of a 2.7 kb transcript in heart, brain, and placenta.

In situ analysis of TANGO 215 expression in adult mice revealed expression in the brain (cortex and caudate putamen), kidney (cortex, most likely within the glomeruli), bladder (ubiquitous expression), liver (possibly within vessels), and placenta (outer membrane region). This analysis did not detect expression in the lung, small intestine, pancreas, thymus, eye, heart, or muscle/diaphragm.

In situ analysis of TANGO 215 in embryos revealed expression at E13.5 in developing limbs and vertebrae. At E14.5 the observed expression pattern was similar to that at E13.5 except that expression was observed in the muscle surrounding abdomen, the skin, and the jaw. At E15.5 expression was observed in the developing kidney and bladder and outer layer of the tongue. At later ages, E16.5 through P1.5, expression is observed in the smooth muscle layer of the small intestine, the portal regions of the liver, and the large airways of the lungs. Expression in the brain is absent until E18.5 when expression is apparent in the caudate putamen. Expression remains strong at P1.5 in the vertebrae, tail, and sternum and possibly the muscle between developing bones.

The region of human TANGO 215 from amino acid 280 to the end is predicted to be the human homologue of *Limilus* Factor C (27% identity). Thus, this region of TANGO 215 is predicted to include an effector domain (serine protease domain) and, perhaps, an LPS sensing domain. Thus, TANGO 215 may sense and respond to LPS with the response to the presence of LPS being activation of

serine protease activity. Accordingly, TANGO 215 nucleic acids and polypeptides as well as antibodies directed against TANGO 215 and modulators of TANGO 215 expression or activity may be useful in the diagnosis and treatment sepsis.

CUB domains are extracellular domains of about 110 amino acids. CUB domains are found in functionally diverse, mostly developmentally regulated proteins. Most contain four cysteines that are involved in two disulfide bonds (C1-C2 and C3-C4). SCR domains are also known as complement control protein (CCP) modules. EGF domains are commonly involved in receptor-ligand interactions. CUB, EGF, and SCR domains are commonly involved in protein-protein interaction. Because these domains are present in TANGO 215, it is predicted to interact with one or more other proteins. The presence of these domains in TANGO 215 suggests that TANGO 215 is involved in development, perhaps bone and cartilage morphogenesis. TANGO 215 nucleic acid molecules and polypeptides as well as anti-TANGO 215 antibodies and modulators of TANGO 215 expression or activity may be useful in the treatment of developmental disorders.

TANGO 187

The human TANGO 187-1/3 cDNA of SEQ ID NO:11 has a 1032 nucleotide open reading frame (SEQ ID NO:22) encoding a 343 amino acid protein (SEQ ID NO:33). The cDNA and protein sequences of human TANGO 187-1/3 are shown in Figure 20.

Human TANGO 187-1/3 is predicted to be a wholly secreted protein having a 20 amino acid signal sequence (amino acids 1 - 20 of SEQ ID NO:33; SEQ ID NO:75) followed by a 323 amino acid mature protein (amino acids 21 - 343 of SEQ ID NO:33; SEQ ID NO:87). Human TANGO 187-1/3 is predicted to have a molecular weight of 37.5 kDa prior to cleavage of its signal peptide and a molecular weight of 35.9 kDa subsequent to cleavage of its signal peptide.

The TANGO 187-1/3 cDNA described upon actually represents one of 8 different TANGO 187 splice variants. Each variant contains none, one, two or three of three variant regions. These regions are referred to as region 1, region 2, and region 3, and each of the various forms of TANGO 187 is referred to by including a reference to the variant regions present. Thus, the form of TANGO 187 described above is TANGO 187-1/3 because it includes regions 1 and 3.

Figure 46 depicts the cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of TANGO 187-1.

Figure 47 depicts the cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of TANGO 187-2/3.

Figure 48 depicts the cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of TANGO 187-1/2/3.

Figure 49 depicts the cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of TANGO 187-1/2.

Figure 50 depicts the cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of TANGO 187-2.

Figure 51 depicts the cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of TANGO 187-3.

Figure 52 depicts the cDNA sequence (SEQ ID NO:__) and predicted amino acid sequence (SEQ ID NO:__) of TANGO 187. This form does not include any of the three variant regions.

The murine TANGO 187 cDNA of SEQ ID NO:43 is only a partial sequence. This cDNA has an open reading frame extending from nucleotide 73 to the end of the available sequence (SEQ ID NO:53) encoding a 152 amino acid protein (SEQ ID NO:63). The partial cDNA and protein sequences of murine TANGO 187 are shown in Figure 21.

Figure 31 depicts an alignment of the predicted amino acid sequences of human (SEQ ID NO:33) and murine (SEQ ID NO:63; partial) TANGO 187 (50.4% identity). Figure 41 depicts an alignment of the cDNA sequences of human (SEQ ID NO:11) and murine (SEQ ID NO:43; partial) TANGO 187 (66.0% identity).

Northern analysis of human TANGO 187 mRNA expression revealed the presence of 1.3 and 2.4 kb transcripts that are approximately equally expressed at a low level in heart, brain, lung, liver, and smooth muscle and at a moderate level in kidney and placenta.

In situ analysis of TANGO 187 expression in adult mice revealed that TANGO 187 is expressed in brain (weak, ubiquitous signal), eye and harderian gland (weak signal in the retina), submandibular gland (weak, ubiquitous signal), stomach (weak, ubiquitous signal), kidney (weak,

ubiquitous signal), adrenal gland (low level, ubiquitous expression), colon (low level, ubiquitous expression), small intestine (low level, ubiquitous expression), thymus (moderate level, ubiquitous expression in the cortical region with lower expression in the medulla), lymph node (ubiquitous expression), spleen (low level ubiquitous expression with lower expression in the follicles, bladder (moderate expression in the mucosal epithelium), testes (moderate, ubiquitous expression signal that defines the seminiferous vesicles). In this analysis, TANGO 187 expression was not detectable in the spinal cord, brown fat, heart, lung, liver, pancreas, skeletal muscle, and ovaries.

In situ analysis of TANGO 187 expression in embryos at E13.5 revealed ubiquitous expression with the strongest expression in the brain and spinal cord. A punctate expression pattern was observed in the lungs suggestive of higher expression in the developing large airways. At E14.5 the expression pattern was similar to that observed at E13.5 except that expression was observed in the developing olfactory system and the eye at a level similar to that observed in the brain and spinal cord. Expression is also present at E14.5 in the epithelium of the tongue, the dermis of the snout, the kidneys and the stomach. At E15.5 low level ubiquitous expression was observed with the highest expression in the brain, spinal cord, eye, and olfactory system. Slightly lower expression was observed in the lung (ubiquitous expression) and kidney (cortical region) than in the aforementioned neuronal tissues. At E16.5 the observed expression pattern is identical to that seen at E15.5 except TANGO 187 expression is observed in the thymus and the mucosal portion of the stomach. At E18.5 TANGO 187 continues to be highest in neuronal tissue with lower expression in the hind brain and spinal cord than in the

forebrain with the neopallial cortex having the highest signal. At E16.5 expression is observed in the thymus and small intestine. At P1.5 the observed expression pattern is nearly identical to that at E18.5 except that expression in the the lung and stomach has decreased. At P1.5 expression is highest in the brain, eye, olfactory epithelium and kidney.

Tango 187 contain a region moderately similar to an armadillo/beta-catenin repeat. Such repeats are thought to be involved in protein-protein interactions.

TABLE 1: Summary of Human TANGO 180, TANGO 181, TANGO 182, TANGO 183, TANGO 184, TANGO 185, TANGO 186, TANGO 187, TANGO 188, TANGO 189, and TANGO 215 Sequence Information.

Gene	cDNA	ORF	Protein	Fig.	Accession No.
TANGO 180	SEQ ID NO:1	SEQ ID NO:12	SEQ ID NO:23	Fig. 1	ATCC 98900
TANGO 181	SEQ ID NO:2	SEQ ID NO:13	SEQ ID NO:24	Fig. 3	ATCC 98900
TANGO 182	SEQ ID NO:3	SEQ ID NO:14	SEQ ID NO:25	Fig. 5	ATCC 98900
TANGO 183	SEQ ID NO:4	SEQ ID NO:15	SEQ ID NO:26	Fig. 7	ATCC 98900
TANGO 184	SEQ ID NO:5	SEQ ID NO:16	SEQ ID NO:27	Fig. 9	ATCC 98900
TANGO 185	SEQ ID NO:6	SEQ ID NO:17	SEQ ID NO:28	Fig. 11	ATCC 98901
TANGO 186	SEQ ID NO:7	SEQ ID NO:18	SEQ ID NO:29	Fig. 13	ATCC 98901
TANGO 188	SEQ ID NO:8	SEQ ID NO:19	SEQ ID NO:30	Fig. 15	ATCC 98901
TANGO 189	SEQ ID NO:9	SEQ ID NO:20	SEQ ID NO:31	Fig. 17	ATCC 98901
TANGO 215	SEQ ID NO:10	SEQ ID NO:21	SEQ ID NO:32	Fig. 19	ATCC 98899
TANGO 187-1/3	SEQ ID NO:11	SEQ ID NO:22	SEQ ID NO:33	Fig. 20	ATCC 98901
TANGO 187-1	SEQ ID NO:__	SEQ ID NO:__	SEQ ID NO:__	Fig. 46	ATCC ____
TANGO 187-2/3	SEQ ID NO:__	SEQ ID NO:__	SEQ ID NO:__	Fig. 47	ATCC ____
TANGO 187-1/2/3	SEQ ID NO:__	SEQ ID NO:__	SEQ ID NO:__	Fig. 48	ATCC ____
TANGO 187-1/2	SEQ ID NO:__	SEQ ID NO:__	SEQ ID NO:__	Fig. 49	ATCC ____
TANGO 187-2	SEQ ID NO:__	SEQ ID NO:__	SEQ ID NO:__	Fig. 50	ATCC ____
TANGO 187-3	SEQ ID NO:__	SEQ ID NO:__	SEQ ID NO:__	Fig. 51	ATCC ____

TABLE 2: Summary of Domains of Human TANGO 180, TANGO 181, TANGO 182, TANGO 183, TANGO 184, TANGO 185, TANGO 186, TANGO 187, TANGO 188, TANGO 189, and TANGO 215.

Protein	Signal Sequence	Mature Protein	Extracellular Domain	Transmembrane Domain	Cytoplasmic Domain
TANGO 180	aa 1-22 SEQ ID NO:64	aa 23-189 SEQ ID NO:76	-	-	-
TANGO 181	aa 1-22 SEQ ID NO:65	aa 23-339 SEQ ID NO:77	-	-	-
TANGO 182	aa 1-23 SEQ ID NO:66	aa 24-348 SEQ ID NO:78	-	-	-
TANGO 183	aa 1-20 SEQ ID NO:67	aa 21-183 SEQ ID NO:79	aa 21-89 SEQ ID NO:88	aa 90-112 SEQ ID NO:94	aa 113-183 SEQ ID NO:102
TANGO 184	aa 1-28 SEQ ID NO:68	aa 29-198 SEQ ID NO:80	aa 29-102 SEQ ID NO:89	aa 103-125 SEQ ID NO:95	aa 126-198 SEQ ID NO:103
TANGO 185	aa 1-24 SEQ ID NO:69	aa 25-193 SEQ ID NO:81	aa 25-75 SEQ ID NO:90 and aa 131-150 SEQ ID NO:91	aa 76-102 SEQ ID NO:96 and aa 110-131 SEQ ID NO:97 and aa 151-174 SEQ ID NO:98	aa 103-109 SEQ ID NO:104 and aa 175-193 SEQ ID NO:105
TANGO 186	aa 1-20 SEQ ID NO:70	aa 21-383 SEQ ID NO:82	-	-	-
TANGO 188	aa 1-23 SEQ ID NO:71	aa 24-264 SEQ ID NO:83	-	-	-

TANGO 189	aa 1-24 SEQ ID NO:72 or aa 1-25 SEQ ID NO:73	aa 25-251 SEQ ID NO:84 or aa 26-251 SEQ ID NO:85	aa 25-138 SEQ ID NO:92 or aa 26-138 SEQ ID NO:93 and aa 196-211 SEQ ID NO:108	aa 139-164 SEQ ID NO:99 and aa 178-195 SEQ ID NO:100 and aa 212-237 SEQ ID NO:101	aa 165-177 SEQ ID NO:106 and aa 238-253 SEQ ID NO:107
TANGO 215	aa 1-21 SEQ ID NO:74	aa 22-720 SEQ ID NO:86	-	-	-
TANGO 187-1/3	aa 1-20 SEQ ID NO:75	aa 21-343 SEQ ID NO:87	-	-	-

TABLE 3: Summary of Murine TANGO 180, TANGO 180, TANGO 181, TANGO 182, TANGO 183, TANGO 184, TANGO 185, TANGO 186, TANGO 188, TANGO 189, and TANGO 187 Sequence Information

Gene	cDNA	ORF	Protein	Figure	AA align. with human	NA align. with human
TANGO 180	SEQ ID NO:34	SEQ ID NO:44	SEQ ID NO:54	Fig. 2	Fig. 22	Fig. 32
TANGO 181 (partial)	SEQ ID NO:35	SEQ ID NO:45	SEQ ID NO:55	Fig. 4	Fig. 23	Fig. 33
TANGO 182 (partial)	SEQ ID NO:36	SEQ ID NO:46	SEQ ID NO:56	Fig. 6	Fig. 24	Fig. 34
TANGO 183	SEQ ID NO:37	SEQ ID NO:47	SEQ ID NO:57	Fig. 8	Fig. 25	Fig. 35
TANGO 184	SEQ ID NO:38	SEQ ID NO:48	SEQ ID NO:58	Fig. 10	Fig. 26	Fig. 36
TANGO 185	SEQ ID NO:39	SEQ ID NO:49	SEQ ID NO:59	Fig. 12	Fig. 27	Fig. 37
TANGO 186	SEQ ID NO:40	SEQ ID NO:50	SEQ ID NO:60	Fig. 14	Fig. 28	Fig. 38
TANGO 188	SEQ ID NO:41	SEQ ID NO:51	SEQ ID NO:61	Fig. 16	Fig. 29	Fig. 39
TANGO 189	SEQ ID NO:42	SEQ ID NO:52	SEQ ID NO:62	Fig. 18	Fig. 30	Fig. 40
TANGO 187 (partial)	SEQ ID NO:43	SEQ ID NO:53	SEQ ID NO:63	Fig. 21	Fig. 31	Fig. 41

TANGO 181	SEQ ID NO:__	SEQ ID NO:__	SEQ ID NO:__	Fig. 53		
TANGO 182	SEQ ID NO:__	SEQ ID NO:__	SEQ ID NO:__	Fig. 54		
TANGO 187	SEQ ID NO:__	SEQ ID NO:__	SEQ ID NO:__	Fig. 55		
TANGO 215	SEQ ID NO:__	SEQ ID NO:__	SEQ ID NO:__	Fig. 56		

Various aspects of the invention are described in further detail in the following subsections

I. Isolated Nucleic Acid Molecules

One aspect of the invention pertains to isolated nucleic acid molecules that encode a polypeptide of the invention or a biologically active portion thereof, as well as nucleic acid molecules sufficient for use as hybridization probes to identify nucleic acid molecules encoding a polypeptide of the invention and fragments of such nucleic acid molecules suitable for use as PCR primers for the amplification or mutation of nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (e.g., cDNA or genomic DNA) and RNA molecules (e.g., mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Preferably, an "isolated" nucleic acid molecule is free of sequences (preferably protein encoding sequences) which naturally flank the nucleic

acid (i.e., sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kB, 4 kB, 3 kB, 2 kB, 1 kB, 0.5 kB or 0.1 kB of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the present invention, e.g., a nucleic acid molecule having the nucleotide sequence of any of SEQ ID Nos:1-22, 34-43, and __ - ___ or the cDNA of a clone deposited as any of ATCC 98899, 98900, and 989001, or a complement thereof, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or a portion of the nucleic acid sequences of any of SEQ ID NOs:1-22, 34-43, and __ - ___ or the cDNA of a clone deposited as any of ATCC 98899, 98900, and 989001 as a hybridization probe, nucleic acid molecules of the invention can be isolated using standard hybridization and cloning techniques (e.g., as described in Sambrook et al., eds., *Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

A nucleic acid molecule of the invention can be amplified using cDNA, mRNA or genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore,

oligonucleotides corresponding to all or a portion of a nucleic acid molecule of the invention can be prepared by standard synthetic techniques, e.g., using an automated DNA synthesizer.

In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which is a complement of the nucleotide sequence shown in SEQ ID NOs:1-22, 34-43, and ___ - ___ or the cDNA of a clone deposited as ATCC 98899, 98900, and 989001, or a portion thereof. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given nucleotide sequence thereby forming a stable duplex.

Moreover, a nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence encoding a full length polypeptide of the invention for example, a fragment which can be used as a probe or primer or a fragment encoding a biologically active portion of a polypeptide of the invention. The nucleotide sequence determined from the cloning one gene allows for the generation of probes and primers designed for use in identifying and/or cloning homologues in other cell types, e.g., from other tissues, as well as homologues from other mammals. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, preferably about 25, more preferably about 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 or 400 consecutive nucleotides of the sense or anti-sense sequence of any of SEQ ID NOs:1-22, 34-43, and __ - __ or the cDNA of a clone deposited as ATCC 98899, 98900, and 989001 or of a naturally occurring mutant of any of SEQ NOs:1-22, 34-43, and ___ - ___ or

the cDNA of a clone deposited as ATCC 98899, 98900, and 989001.

Probes based on the sequence of a nucleic acid molecule of the invention can be used to detect transcripts or genomic sequences encoding the same protein molecule encoded by a selected nucleic acid molecule. The probe comprises a label group attached thereto, e.g., a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as part of a diagnostic test kit for identifying cells or tissues which mis-express the protein, such as by measuring levels of a nucleic acid molecule encoding the protein in a sample of cells from a subject, e.g., detecting mRNA levels or determining whether a gene encoding the protein has been mutated or deleted.

A nucleic acid fragment encoding a "biologically active portion" of a polypeptide of the invention can be prepared by isolating a portion of any of SEQ ID NOs:1-22, 34-43, and ___ - ___ or the nucleotide sequence of the cDNA of a clone deposited as ATCC 98899, 98900, and 989001 which encodes a polypeptide having a biological activity, expressing the encoded portion of the polypeptide protein (e.g., by recombinant expression *in vitro*) and assessing the activity of the encoded portion of the polypeptide.

The invention further encompasses nucleic acid molecules that differ from the nucleotide sequence of SEQ ID NOs:1-22, 34-43, and __ - ___ or the cDNA of a clone of ATCC 98899, 98900, and 989001 due to degeneracy of the genetic code and thus encode the same protein as that encoded by the nucleotide sequence shown in any of SEQ ID NOs:1-22, 34-43 , and ___ - ___ or the cDNA of a clone deposited as ATCC 98899, 98900, and 989001.

In addition to the nucleotide sequences shown in SEQ ID NOs:1-22, 34-43, and ___ - ___ and present in cDNA's of

the clones deposited of ATCC 98899, 98900, and 989001, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequence may exist within a population (e.g., the human population). Such genetic polymorphisms may exist among individuals within a population due to natural allelic variation. An allele is one of a group of genes which occur alternatively at a given genetic locus. As used herein, the phrase "allelic variant" refers to a nucleotide sequence which occurs at a given locus or to a polypeptide encoded by the nucleotide sequence. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding a polypeptide of the invention. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

Moreover, nucleic acid molecules encoding proteins of the invention from other species (homologues), which have a nucleotide sequence which differs from that of the human protein described herein are intended to be within the scope of the invention. Nucleic acid molecules corresponding to natural allelic variants and homologues of a cDNA of the invention can be isolated based on their identity to the human nucleic acid molecule disclosed herein using the human cDNAs, or a portion thereof, as a hybridization probe according to standard hybridization

techniques under stringent hybridization conditions. For example, a cDNA encoding a soluble form of a membrane-bound protein of the invention isolated based on its hybridization to a nucleic acid molecule encoding all or part of the membrane-bound form. Likewise, a cDNA encoding a membrane-bound form can be isolated based on its hybridization to a nucleic acid molecule encoding all or part of the soluble form.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 300 (325, 350, 375, 400, 425, 450, 500, 550, 600, 650, 700, 800, 900, 1000, or 1290) nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence, preferably the coding sequence, of any of SEQ ID NOs:1-22, 34-43, and ___ - ___ the cDNA of a clone deposited as ATCC 98899, 98900, and 989001, or a complement thereof.

As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% (65%, 70%, preferably 75%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50-65°C. Preferably, an isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to the sequence of any of SEQ ID NOs:1-22, 34-43, and ___ - ___, the cDNA of ATCC 98899, 98900, and 989001, or the complement thereof, corresponds to a naturally-occurring nucleic acid molecule. As used

herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (e.g., encodes a natural protein).

In addition to naturally-occurring allelic variants of a nucleic acid molecule of the invention sequence that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation thereby leading to changes in the amino acid sequence of the encoded protein, without altering the biological activity of the protein. For example, one can make nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are not conserved or only semi-conserved among homologues of various species may be non-essential for activity and thus would be likely targets for alteration. Alternatively, amino acid residues that are conserved among the homologues of various species (e.g., murine and human) may be essential for activity and thus would not be likely targets for alteration. Conserved cysteine residues are particularly important and are preferably retained in functional variants

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a polypeptide of the invention that contain changes in amino acid residues that are not essential for activity. Such polypeptides differ in amino acid sequence from SEQ ID NOs:23-33, 54-63, and __ - ___ yet retain biological activity. In one embodiment, the isolated nucleic acid molecule includes a nucleotide sequence encoding a

protein that includes an amino acid sequence that is at least about 45% identical, 65%, 75%, 85%, 95%, or 98% identical to the amino acid sequence of any of SEQ ID Nos:23-3, 54-63, and ___ - ___.

An isolated nucleic acid molecule encoding a variant protein can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of SEQ ID NOs:1-22, 34-43, and __ - ___ the cDNA of a clone deposited of ATCC 98899, 98900, and 989001 such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein. Mutations can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded

protein can be expressed recombinantly and the activity of the protein can be determined.

In a preferred embodiment, a mutant polypeptide that is a variant of a polypeptide of the invention can be assayed for: (1) the ability to form protein:protein interactions with proteins in a signalling pathway of the polypeptide of the invention; (2) the ability to bind a ligand of the polypeptide of the invention; or (3) the ability to bind to an intracellular target protein of the polypeptide of the invention. In yet another preferred embodiment, the mutant polypeptide can be assayed for the ability to modulate cellular proliferation or cellular differentiation.

The present invention encompasses antisense nucleic acid molecules, i.e., molecules which are complementary to a sense nucleic acid encoding a polypeptide of the invention, e.g., complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. Accordingly, an antisense nucleic acid can hydrogen bond to a sense nucleic acid. The antisense nucleic acid can be complementary to an entire coding strand, or to only a portion thereof, e.g., all or part of the protein coding region (or open reading frame). An antisense nucleic acid molecule can be antisense to all or part of a noncoding region of the coding strand of a nucleotide sequence encoding a polypeptide of the invention. The noncoding regions ("5' and 3' untranslated regions") are the 5' and 3' sequences which flank the coding region and are not translated into amino acids.

An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art.

For example, an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a selected polypeptide of the invention to thereby inhibit expression, e.g., by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, e.g., by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

An antisense nucleic acid molecule of the invention can be an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gaultier et al. (1987) *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a

2'-o-methylribonucleotide (Inoue et al. (1987) *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue et al. (1987) *FEBS Lett.* 215:327-330).

The invention also encompasses ribozymes. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (e.g., hammerhead ribozymes (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. A ribozyme having specificity for a nucleic acid molecule encoding a polypeptide of the invention can be designed based upon the nucleotide sequence of a cDNA disclosed herein. For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a Cech et al. U.S. Patent No. 4,987,071; and Cech et al. U.S. Patent No. 5,116,742. Alternatively, an mRNA encoding a polypeptide of the invention can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. *See, e.g.*, Bartel and Szostak (1993) *Science* 261:1411-1418.

The invention also encompasses nucleic acid molecules which form triple helical structures. For example, expression of a polypeptide of the invention can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the gene encoding the polypeptide (e.g., the promoter and/or enhancer) to form triple helical structures that prevent transcription of the gene in target cells. *See generally* Helene (1991) *Anticancer Drug Des.* 6(6):569-84; Helene (1992) *Ann. N.Y.*

Acad. Sci. 660:27-36; and Maher (1992) *Bioassays* 14(12):807-15.

In preferred embodiments, the nucleic acid molecules of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, e.g., the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (*see* Hyrup et al. (1996) *Bioorganic & Medicinal Chemistry* 4(1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, e.g., DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup et al. (1996), *supra*; Perry-O'Keefe et al. (1996) *Proc. Natl. Acad. Sci. USA* 93: 14670-675.

PNAs can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, e.g., inducing transcription or translation arrest or inhibiting replication. PNAs can also be used, e.g., in the analysis of single base pair mutations in a gene by, e.g., PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, e.g., S1 nucleases (Hyrup (1996), *supra*; or as probes or primers for DNA sequence and hybridization (Hyrup (1996), *supra*; Perry-O'Keefe et al. (1996) *Proc. Natl. Acad. Sci. USA* 93: 14670-675).

In another embodiment, PNAs can be modified, e.g., to enhance their stability or cellular uptake, by attaching

lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated which may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, e.g., RNAse H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup (1996), *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996), *supra*, and Finn et al. (1996) *Nucleic Acids Res.* 24(17):3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite can be used as a link between the PNA and the 5' end of DNA (Mag et al. (1989) *Nucleic Acids Res.* 17:5973-88). PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn et al. (1996) *Nucleic Acids Res.* 24(17):3357-63). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser et al. (1975) *Bioorganic Med. Chem. Lett.* 5:1119-11124).

In other embodiments, the oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (*see, e.g.*, Letsinger et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:648-652; PCT Publication No. W0 88/09810) or

the blood-brain barrier (*see, e.g.*, PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (*see, e.g.*, Krol et al. (1988) *Bio/Techniques* 6:958-976) or intercalating agents (*see, e.g.*, Zon (1988) *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

II. Isolated Proteins and Antibodies

One aspect of the invention pertains to isolated proteins, and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a polypeptide of the invention. In one embodiment, the native polypeptide can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, polypeptides of the invention are produced by recombinant DNA techniques. Alternative to recombinant expression, a polypeptide of the invention can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is substantially free of cellular material includes

preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, i.e., it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

Biologically active portions of a polypeptide of the invention include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the protein (e.g., the amino acid sequence shown in any of SEQ ID Nos:23-33, 54-63, and ___-___ which include fewer amino acids than the full length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding protein. A biologically active portion of a protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of a polypeptide of the invention.

Preferred polypeptides have the amino acid sequence of any of SEQ ID Nos:23-33, 54-63, and ___ - ___. Other useful proteins are substantially identical (e.g., at least about 45%, preferably 55%, 65%, 75%, 85%, 95%, or 99%) to any of SEQ ID Nos:22-33, 54-63, and ___ - ___ and retain the functional activity of the protein of the corresponding naturally-occurring protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

To determine the percent identity of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity = # of identical positions/total # of positions (e.g., overlapping positions) x 100). Preferably, the two sequences are the same length.

The determination of percent homology between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, et al. (1990) *J.*

Mol. Biol. 215:403-410. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. (1997) *Nucleic Acids Res.* 25:3389-3402. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules. *Id.* When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. *See* http://www.ncbi.nlm.nih.gov. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) *CABIOS* 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

The invention also provides chimeric or fusion proteins. As used herein, a "chimeric protein" or "fusion protein" comprises all or part (preferably biologically active) of a polypeptide of the invention operably linked to a heterologous polypeptide (i.e., a polypeptide other than the same polypeptide of the

invention). Within the fusion protein, the term "operably linked" is intended to indicate that the polypeptide of the invention and the heterologous polypeptide are fused in-frame to each other. The heterologous polypeptide can be fused to the N-terminus or C-terminus of the polypeptide of the invention.

One useful fusion protein is a GST fusion protein in which the polypeptide of the invention is fused to the C-terminus of GST sequences. Such fusion proteins can facilitate the purification of a recombinant polypeptide of the invention.

In another embodiment, the fusion protein contains a heterologous signal sequence at its N-terminus. For example, the native signal sequence of a polypeptide of the invention can be removed and replaced with a signal sequence from another protein. For example, the gp67 secretory sequence of the baculovirus envelope protein can be used as a heterologous signal sequence (*Current Protocols in Molecular Biology*, Ausubel et al., eds., John Wiley & Sons, 1992). Other examples of eukaryotic heterologous signal sequences include the secretory sequences of melittin and human placental alkaline phosphatase (Stratagene; La Jolla, California). In yet another example, useful prokaryotic heterologous signal sequences include the phoA secretory signal (Sambrook et al., *supra*) and the protein A secretory signal (Pharmacia Biotech; Piscataway, New Jersey).

In yet another embodiment, the fusion protein is an immunoglobulin fusion protein in which all or part of a polypeptide of the invention is fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a ligand (soluble or membrane-bound)

and a protein on the surface of a cell (receptor), to thereby suppress signal transduction *in vivo*. The immunoglobulin fusion protein can be used to affect the bioavailability of a cognate ligand of a polypeptide of the invention. Inhibition of ligand/receptor interaction may be useful therapeutically, both for treating proliferative and differentiative disorders and for modulating (e.g. promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies directed against a polypeptide of the invention in a subject, to purify ligands and in screening assays to identify molecules which inhibit the interaction of receptors with ligands.

Chimeric and fusion protein of the invention can be produced by standard recombinant DNA techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and reamplified to generate a chimeric gene sequence (*see, e.g.*, Ausubel et al., *supra*). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST polypeptide). A nucleic acid encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide of the invention.

A signal sequence of a polypeptide of the invention (SEQ ID NOs:64-75) can be used to facilitate secretion and isolation of the secreted protein or other proteins of interest. Signal sequences are typically characterized by a core of hydrophobic amino acids which

are generally cleaved from the mature protein during secretion in one or more cleavage events. Such signal peptides contain processing sites that allow cleavage of the signal sequence from the mature proteins as they pass through the secretory pathway. Thus, the invention pertains to the described polypeptides having a signal sequence, as well as to the signal sequence itself and to the polypeptide in the absence of the signal sequence (i.e., the cleavage products). In one embodiment, a nucleic acid sequence encoding a signal sequence of the invention can be operably linked in an expression vector to a protein of interest, such as a protein which is ordinarily not secreted or is otherwise difficult to isolate. The signal sequence directs secretion of the protein, such as from a eukaryotic host into which the expression vector is transformed, and the signal sequence is subsequently or concurrently cleaved. The protein can then be readily purified from the extracellular medium by art recognized methods. Alternatively, the signal sequence can be linked to the protein of interest using a sequence which facilitates purification, such as with a GST domain.

In another embodiment, the signal sequences of the present invention can be used to identify regulatory sequences, e.g., promoters, enhancers, repressors. Since signal sequences are the most amino-terminal sequences of a peptide, it is expected that the nucleic acids which flank the signal sequence on its amino-terminal side will be regulatory sequences which affect transcription. Thus, a nucleotide sequence which encodes all or a portion of a signal sequence can be used as a probe to identify and isolate signal sequences and their flanking regions, and these flanking regions can be studied to identify regulatory elements therein.

The present invention also pertains to variants of the polypeptides of the invention. Such variants have an altered amino acid sequence which can function as either agonists (mimetics) or as antagonists. Variants can be generated by mutagenesis, e.g., discrete point mutation or truncation. An agonist can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of the protein. An antagonist of a protein can inhibit one or more of the activities of the naturally occurring form of the protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the protein of interest. Thus, specific biological effects can be elicited by treatment with a variant of limited function. Treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein can have fewer side effects in a subject relative to treatment with the naturally occurring form of the protein.

Variants of a protein of the invention which function as either agonists (mimetics) or as antagonists can be identified by screening combinatorial libraries of mutants, e.g., truncation mutants, of the protein of the invention for agonist or antagonist activity. In one embodiment, a variegated library of variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential protein sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (e.g., for phage display). There are a variety of methods which can be used to produce libraries of potential variants of the

polypeptides of the invention from a degenerate oligonucleotide sequence. Methods for synthesizing degenerate oligonucleotides are known in the art (*see, e.g.*, Narang (1983) *Tetrahedron* 39:3; Itakura et al. (1984) *Annu. Rev. Biochem.* 53:323; Itakura et al. (1984) *Science* 198:1056; Ike et al. (1983) *Nucleic Acid Res.* 11:477).

In addition, libraries of fragments of the coding sequence of a polypeptide of the invention can be used to generate a variegated population of polypeptides for screening and subsequent selection of variants. For example, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of the coding sequence of interest with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes N-terminal and internal fragments of various sizes of the protein of interest.

Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates

isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify variants of a protein of the invention (Arkin and Yourvan (1992) *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave et al. (1993) *Protein Engineering* 6(3):327-331).

An isolated polypeptide of the invention, or a fragment thereof, can be used as an immunogen to generate antibodies using standard techniques for polyclonal and monoclonal antibody preparation. The full-length polypeptide or protein can be used or, alternatively, the invention provides antigenic peptide fragments for use as immunogens. The antigenic peptide of a protein of the invention comprises at least 8 (preferably 10, 15, 20, or 30) amino acid residues of the amino acid sequence shown in any of SEQ ID Nos:23-33, 54-64, and ___ - ___ and encompasses an epitope of the protein such that an antibody raised against the peptide forms a specific immune complex with the protein.

Preferred epitopes encompassed by the antigenic peptide are regions that are located on the surface of the protein, e.g., hydrophilic regions, rather than hydrophobic regions, e.g., transmembrane domains. The hydrophilicity of a protein sequence can be easily determined using readily available programs.

An immunogen typically is used to prepare antibodies by immunizing a suitable subject, (e.g., rabbit, goat, mouse or other mammal). An appropriate immunogenic preparation can contain, for example, recombinantly expressed chemically synthesized polypeptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar immunostimulatory agent.

Accordingly, another aspect of the invention pertains to antibodies directed against a polypeptide of the invention. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site which specifically binds an antigen, such as a polypeptide of the invention. A molecule which specifically binds to a given polypeptide of the invention is a molecule which binds the polypeptide, but does not substantially bind other molecules in a sample, e.g., a biological sample, which naturally contains the polypeptide. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and $F(ab')_2$ fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope.

Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a polypeptide of the invention as an immunogen. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If desired, the antibody molecules can be isolated from the mammal (e.g., from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, e.g., when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques,

such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497, the human B cell hybridoma technique (Kozbor et al. (1983) *Immunol. Today* 4:72), the EBV-hybridoma technique (Cole et al. (1985), *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing hybridomas is well known (*see generally Current Protocols in Immunology* (1994) Coligan et al. (eds.) John Wiley & Sons, Inc., New York, NY). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, e.g., using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™ Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs et al. (1991) *Bio/Technology* 9:1370-1372; Hay et al. (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse et al. (1989) *Science*

246:1275-1281; Griffiths et al. (1993) *EMBO J.* 12:725-734.

Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better et al. (1988) *Science* 240:1041-1043; Liu et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu et al. (1987) *J. Immunol.* 139:3521-3526; Sun et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura et al. (1987) *Canc. Res.* 47:999-1005; Wood et al. (1985) *Nature* 314:446-449; and Shaw et al. (1988) *J. Natl. Cancer Inst.* 80:1553-1559); Morrison (1985) *Science* 229:1202-1207; Oi et al. (1986) *Bio/Techniques* 4:214; U.S. Patent 5,225,539; Jones et al. (1986) *Nature* 321:552-525; Verhoeyan et al. (1988) *Science* 239:1534; and Beidler et al. (1988) *J. Immunol.* 141:4053-4060.

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Such antibodies can be produced using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained using conventional hybridoma technology. The

human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995, *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, *see, e.g.*, U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope.

An antibody directed against a polypeptide of the invention (e.g., monoclonal antibody) can be used to isolate the polypeptide by standard techniques, such as affinity chromatography or immunoprecipitation. Moreover, such an antibody can be used to detect the protein (e.g., in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the polypeptide. The antibodies can also be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, e.g., to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the

antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

III. Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a polypeptide of the invention (or a portion thereof). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are

replicated along with the host genome. Moreover, certain vectors, expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids (vectors). However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (e.g., in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and those which direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences). It will be appreciated by those skilled in

the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

The recombinant expression vectors of the invention can be designed for expression of a polypeptide of the invention in prokaryotic or eukaryotic cells, e.g., bacterial cells such as *E. coli*, insect cells (using baculovirus expression vectors), yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase.

Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson (1988) *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann et al., (1988) *Gene* 69:301-315) and pET 11d (Studier et al., *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 60-89). Target gene expression from the pTrc vector relies on host RNA polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a coexpressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident λ prophage harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 119-128). Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada et al. (1992) *Nucleic Acids Res.* 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the expression vector is a yeast expression vector. Examples of vectors for expression in

yeast *S. cerivisae* include pYepSec1 (Baldari et al. (1987) *EMBO J.* 6:229-234), pMFa (Kurjan and Herskowitz, (1982) *Cell* 30:933-943), pJRY88 (Schultz et al. (1987) *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, CA), and pPicZ (Invitrogen Corp, San Diego, CA).

Alternatively, the expression vector is a baculovirus expression vector. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., Sf 9 cells) include the pAc series (Smith et al. (1983) *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers (1989) *Virology* 170:31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed (1987) *Nature* 329:840) and pMT2PC (Kaufman et al. (1987) *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook et al., *supra*.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert et al. (1987) *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame and Eaton (1988) *Adv. Immunol.* 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore (1989) *EMBO J.* 8:729-733) and immunoglobulins (Banerji et

al. (1983) *Cell* 33:729-740; Queen and Baltimore (1983) *Cell* 33:741-748), neuron-specific promoters (e.g., the neurofilament promoter; Byrne and Ruddle (1989) *Proc. Natl. Acad. Sci. USA* 86:5473-5477), pancreas-specific promoters (Edlund et al. (1985) *Science* 230:912-916), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, for example the murine hox promoters (Kessel and Gruss (1990) *Science* 249:374-379) and the α-fetoprotein promoter (Campes and Tilghman (1989) *Genes Dev.* 3:537-546).

The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operably linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to the mRNA encoding a polypeptide of the invention. Regulatory sequences operably linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub et al. (*Reviews - Trends in Genetics*, Vol. 1(1) 1986).

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic (e.g., *E. coli*) or eukaryotic (e.g., an insect cell, a yeast cell or a mammalian cell) cell.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, et al. (*supra*), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (e.g., for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs,

such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (e.g., cells that have incorporated the selectable marker gene will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce a polypeptide of the invention. Accordingly, the invention further provides methods for producing a polypeptide of the invention using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding a polypeptide of the invention has been introduced) in a suitable medium such that the polypeptide is produced. In another embodiment, the method further comprises isolating the polypeptide from the medium or the host cell.

The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which a sequences encoding a polypeptide of the invention have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous sequences encoding a polypeptide of the invention have been introduced into their genome or homologous recombinant animals in which endogenous encoding a polypeptide of the invention sequences have been altered. Such animals are useful for studying the function and/or activity of the polypeptide and for identifying and/or evaluating modulators of polypeptide activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals

include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, e.g., an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing nucleic acid encoding a polypeptide of the invention (or a homologue thereof) into the male pronuclei of a fertilized oocyte, e.g., by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the polypeptide of the invention to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent NOS. 4,736,866 and 4,870,009, U.S. Patent No. 4,873,191 and in Hogan, *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence

of the transgene in its genome and/or expression of mRNA encoding the transgene in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying the transgene can further be bred to other transgenic animals carrying other transgenes.

To create an homologous recombinant animal, a vector is prepared which contains at least a portion of a gene encoding a polypeptide of the invention into which a deletion, addition or substitution has been introduced to thereby alter, e.g., functionally disrupt, the gene. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous gene is functionally disrupted (i.e., no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous gene is mutated or otherwise altered but still encodes functional protein (e.g., the upstream regulatory region can be altered to thereby alter the expression of the endogenous protein). In the homologous recombination vector, the altered portion of the gene is flanked at its 5' and 3' ends by additional nucleic acid of the gene to allow for homologous recombination to occur between the exogenous gene carried by the vector and an endogenous gene in an embryonic stem cell. The additional flanking nucleic acid sequences are of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (*see, e.g.*, Thomas and Capecchi (1987) *Cell* 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the

introduced gene has homologously recombined with the endogenous gene are selected (*see, e.g.*, Li et al. (1992) *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal (e.g., a mouse) to form aggregation chimeras (*see, e.g.*, Bradley in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, ed. (IRL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley (1991) *Current Opinion in Bio/Technology* 2:823-829 and in PCT Publication NOS. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169.

In another embodiment, transgenic non-human animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, *see, e.g.*, Lakso et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman et al. (1991) *Science* 251:1351-1355. If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one

containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut et al. (1997) *Nature* 385:810-813 and PCT Publication NOS. WO 97/07668 and WO 97/07669.

IV. Pharmaceutical Compositions

The nucleic acid molecules, polypeptides, and antibodies (also referred to herein as "active compounds") of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

The invention includes methods for preparing pharmaceutical compositions for modulating the expression or activity of a polypeptide or nucleic acid of the invention. Such methods comprise formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a polypeptide or nucleic acid of the invention. Such compositions can further include additionl active agents. Thus, the invention further includes methods for preparing a

pharmaceutical composition by formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a polypeptide or nucleic acid of the invention and one or more addtional active compounds.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF; Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition

must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (e.g., a polypeptide or antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which

yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from a pressurized container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include,

for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active

compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

For antibodies, the preferred dosage is 0.1 mg/kg to 100 mg/kg of body weight (generally 10 mg/kg to 20 mg/kg). If the antibody is to act in the brain, a dosage of 50 mg/kg to 100 mg/kg is usually appropriate. Generally, partially human antibodies and fully human antibodies have a longer half-life within the human body than other antibodies. Accordingly, lower dosages and less frequent administration is often possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration (e.g., into the brain). A method for lipidation of antibodies is described by Cruikshank et al. ((1997) *J. Acquired Immune Deficiency Syndromes and Human Retrovirology* 14:193).

The nucleic acid molecules of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Patent 5,328,470) or by stereotactic injection (*see, e.g.,* Chen et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, e.g. retroviral vectors, the pharmaceutical preparation can

include one or more cells which produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

V. Uses and Methods of the Invention

The nucleic acid molecules, proteins, protein homologues, and antibodies described herein can be used in one or more of the following methods: a) screening assays; b) detection assays (e.g., chromosomal mapping, tissue typing, forensic biology); c) predictive medicine (e.g., diagnostic assays, prognostic assays, monitoring clinical trials, and pharmacogenomics); and d) methods of treatment (e.g., therapeutic and prophylactic). For example, polypeptides of the invention can to used to (i) modulate cellular proliferation; (ii) modulate cellular differentiation; and (iii) modulate cell survival. The isolated nucleic acid molecules of the invention can be used to express proteins (e.g., via a recombinant expression vector in a host cell in gene therapy applications), to detect mRNA (e.g., in a biological sample) or a genetic lesion, and to modulate activity of a polypeptide of the invention. In addition, the polypeptides of the invention can be used to screen drugs or compounds which modulate activity or expression of a polypeptide of the invention as well as to treat disorders characterized by insufficient or excessive production of a protein of the invention or production of a form of a protein of the invention which has decreased or aberrant activity compared to the wild type protein. In addition, the antibodies of the invention can be used to detect and isolate a protein of the invention and modulate activity of a protein of the invention.

This invention further pertains to novel agents identified by the above-described screening assays and uses thereof for treatments as described herein.

A. Screening Assays

The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, i.e., candidate or test compounds or agents (e.g., peptides, peptidomimetics, small molecules or other drugs) which bind to polypeptide of the invention or have a stimulatory or inhibitory effect on, for example, expression or activity of a polypeptide of the invention.

In one embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of the membrane-bound form of a polypeptide of the invention or biologically active portion thereof. The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the "one-bead one-compound" library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam (1997) *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:6909; Erb et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann et al. (1994). *J. Med. Chem.* 37:2678; Cho et

al. (1993) *Science* 261:1303; Carrell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and Gallop et al. (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (e.g., Houghten (1992) *Bio/Techniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (U.S. Patent No. 5,223,409), spores (Patent NOS. 5,571,698; 5,403,484; and 5,223,409), plasmids (Cull et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:1865-1869) or phage (Scott and Smith (1990) *Science* 249:386-390; Devlin (1990) *Science* 249:404-406; Cwirla et al. (1990) *Proc. Natl. Acad. Sci. USA* 87:6378-6382; and Felici (1991) *J. Mol. Biol.* 222:301-310).

In one embodiment, an assay is a cell-based assay in which a cell which expresses a membrane-bound form of a polypeptide of the invention, or a biologically active portion thereof, on the cell surface is contacted with a test compound and the ability of the test compound to bind to the polypeptide determined. The cell, for example, can be a yeast cell or a cell of mammalian origin. Determining the ability of the test compound to bind to the polypeptide can be accomplished, for example, by coupling the test compound with a radioisotope or enzymatic label such that binding of the test compound to the polypeptide or biologically active portion thereof can be determined by detecting the labeled compound in a complex. For example, test compounds can be labeled with ^{125}I, ^{35}S, ^{14}C, or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting of radioemmission or by scintillation counting. Alternatively, test compounds can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic

label detected by determination of conversion of an appropriate substrate to product. In a preferred embodiment, the assay comprises contacting a cell which expresses a membrane-bound form of a polypeptide of the invention, or a biologically active portion thereof, on the cell surface with a known compound which binds the polypeptide to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with the polypeptide, wherein determining the ability of the test compound to interact with the polypeptide comprises determining the ability of the test compound to preferentially bind to the polypeptide or a biologically active portion thereof as compared to the known compound.

In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a membrane-bound form of a polypeptide of the invention, or a biologically active portion thereof, on the cell surface with a test compound and determining the ability of the test compound to modulate (e.g., stimulate or inhibit) the activity of the polypeptide or biologically active portion thereof. Determining the ability of the test compound to modulate the activity of the polypeptide or a biologically active portion thereof can be accomplished, for example, by determining the ability of the polypeptide protein to bind to or interact with a target molecule.

Determining the ability of a polypeptide of the invention to bind to or interact with a target molecule can be accomplished by one of the methods described above for determining direct binding. As used herein, a "target molecule" is a molecule with which a selected polypeptide (e.g., a polypeptide of the invention binds or interacts with in nature, for example, a molecule on the surface of a cell which expresses the selected

protein, a molecule on the surface of a second cell, a molecule in the extracellular milieu, a molecule associated with the internal surface of a cell membrane or a cytoplasmic molecule. A target molecule can be a polypeptide of the invention or some other polypeptide or protein. For example, a target molecule can be a component of a signal transduction pathway which facilitates transduction of an extracellular signal (e.g., a signal generated by binding of a compound to a polypeptide of the invention) through the cell membrane and into the cell or a second intercellular protein which has catalytic activity or a protein which facilitates the association of downstream signaling molecules with a polypeptide of the invention. Determining the ability of a polypeptide of the invention to bind to or interact with a target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (e.g., intracellular Ca^{2+}, diacylglycerol, IP3, etc.), detecting catalytic/enzymatic activity of the target on an appropriate substrate, detecting the induction of a reporter gene (e.g., a regulatory element that is responsive to a polypeptide of the invention operably linked to a nucleic acid encoding a detectable marker, e.g. luciferase), or detecting a cellular response, for example, cellular differentiation, or cell proliferation.

In yet another embodiment, an assay of the present invention is a cell-free assay comprising contacting a polypeptide of the invention or biologically active portion thereof with a test compound and determining the ability of the test compound to bind to the polypeptide or biologically active portion thereof. Binding of the test compound to the polypeptide can be determined either

directly or indirectly as described above. In a preferred embodiment, the assay includes contacting the polypeptide of the invention or biologically active portion thereof with a known compound which binds the polypeptide to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with the polypeptide, wherein determining the ability of the test compound to interact with the polypeptide comprises determining the ability of the test compound to preferentially bind to the polypeptide or biologically active portion thereof as compared to the known compound.

In another embodiment, an assay is a cell-free assay comprising contacting a polypeptide of the invention or biologically active portion thereof with a test compound and determining the ability of the test compound to modulate (e.g., stimulate or inhibit) the activity of the polypeptide or biologically active portion thereof. Determining the ability of the test compound to modulate the activity of the polypeptide can be accomplished, for example, by determining the ability of the polypeptide to bind to a target molecule by one of the methods described above for determining direct binding. In an alternative embodiment, determining the ability of the test compound to modulate the activity of the polypeptide can be accomplished by determining the ability of the polypeptide of the invention to further modulate the target molecule. For example, the catalytic/enzymatic activity of the target molecule on an appropriate substrate can be determined as previously described.

In yet another embodiment, the cell-free assay comprises contacting a polypeptide of the invention or biologically active portion thereof with a known compound which binds the polypeptide to form an assay mixture, contacting the assay mixture with a test compound, and

determining the ability of the test compound to interact with the polypeptide, wherein determining the ability of the test compound to interact with the polypeptide comprises determining the ability of the polypeptide to preferentially bind to or modulate the activity of a target molecule.

The cell-free assays of the present invention are amenable to use of both a soluble form or the membrane-bound form of a polypeptide of the invention. In the case of cell-free assays comprising the membrane-bound form of the polypeptide, it may be desirable to utilize a solubilizing agent such that the membrane-bound form of the polypeptide is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton X-100, Triton X-114, Thesit, Isotridecypoly(ethylene glycol ether)n, 3-[(3-cholamidopropyl)dimethylamminio]-1-propane sulfonate (CHAPS), 3-[(3-cholamidopropyl)dimethylamminio]-2-hydroxy-1-propane sulfonate (CHAPSO), or N-dodecyl=N,N-dimethyl-3-ammonio-1-propane sulfonate.

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either the polypeptide of the invention or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to the polypeptide, or interaction of the polypeptide with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided which adds a domain that

allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase fusion proteins or glutathione-S-transferase fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical; St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or A polypeptide of the invention, and the mixture incubated under conditions conducive to complex formation (e.g., at physiological conditions for salt and pH). Following incubation, the beads or microtitre plate wells are washed to remove any unbound components and complex formation is measured either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of binding or activity of the polypeptide of the invention can be determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either the polypeptide of the invention or its target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated polypeptide of the invention or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques well known in the art (e.g., biotinylation kit, Pierce Chemicals; Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with the polypeptide of the invention or target molecules but which do not interfere with binding of the polypeptide of the invention to its target molecule can be derivatized to the wells of the plate, and unbound target or polypeptidede of the invention trapped in the wells by antibody conjugation. Methods

for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the polypeptide of the invention or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the polypeptide of the invention or target molecule.

In another embodiment, modulators of expression of a polypeptide of the invention are identified in a method in which a cell is contacted with a candidate compound and the expression of the selected mRNA or protein (i.e., the mRNA or protein corresponding to a polypeptide or nucleic acid of the invention) in the cell is determined. The level of expression of the selected mRNA or protein in the presence of the candidate compound is compared to the level of expression of the selected mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of expression of the polypeptide of the invention based on this comparison. For example, when expression of the selected mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of the selected mRNA or protein expression. Alternatively, when expression of the selected mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of the selected mRNA or protein expression. The level of the selected mRNA or protein expression in the cells can be determined by methods described herein.

In yet another aspect of the invention, a polypeptide of the inventions can be used as "bait proteins" in a two-hybrid assay or three hybrid assay (*see, e.g.*, U.S.

Patent No. 5,283,317; Zervos et al. (1993) *Cell* 72:223-232; Madura et al. (1993) *J. Biol. Chem.* 268:12046-12054; Bartel et al. (1993) *Bio/Techniques* 14:920-924; Iwabuchi et al. (1993) *Oncogene* 8:1693-1696; and PCT Publication No. WO 94/10300), to identify other proteins, which bind to or interact with the polypeptide of the invention and modulate activity of the polypeptide of the invention. Such binding proteins are also likely to be involved in the propagation of signals by the polypeptide of the inventions as, for example, upstream or downstream elements of a signaling pathway involving the polypeptide of the invention.

This invention further pertains to novel agents identified by the above-described screening assays and uses thereof for treatments as described herein.

B. Detection Assays

Portions or fragments of the cDNA sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome and, thus, locate gene regions associated with genetic disease; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample. These applications are described in the subsections below.

1. Chromosome Mapping

Once the sequence (or a portion of the sequence) of a gene has been isolated, this sequence can be used to map the location of the gene on a chromosome. Accordingly, nucleic acid molecules described herein or fragments thereof, can be used to map the location of the corresponding genes on a chromosome. The mapping of the

sequences to chromosomes is an important first step in correlating these sequences with genes associated with disease.

Briefly, genes can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp in length) from the sequence of a gene of the invention. Computer analysis of the sequence of a gene of the invention can be used to rapidly select primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers can then be used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the gene sequences will yield an amplified fragment. For a review of this technique, see D'Eustachio et al. ((1983) *Science* 220:919-924).

PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular sequence to a particular chromosome. Three or more sequences can be assigned per day using a single thermal cycler. Using the nucleic acid sequences of the invention to design oligonucleotide primers, sublocalization can be achieved with panels of fragments from specific chromosomes. Other mapping strategies which can similarly be used to map a gene to its chromosome include *in situ* hybridization (described in Fan et al. (1990) *Proc. Natl. Acad. Sci. USA* 87:6223-27), pre-screening with labeled flow-sorted chromosomes, and pre-selection by hybridization to chromosome specific cDNA libraries. Fluorescence *in situ* hybridization (FISH) of a DNA sequence to a metaphase chromosomal spread can further be used to provide a precise chromosomal location in one step. For a review of this technique, see Verma et al., (Human Chromosomes: A Manual of Basic Techniques (Pergamon Press, New York, 1988)).

Reagents for chromosome mapping can be used individually to mark a single chromosome or a single site on that chromosome, or panels of reagents can be used for marking multiple sites and/or multiple chromosomes. Reagents corresponding to noncoding regions of the genes actually are preferred for mapping purposes. Coding sequences are more likely to be conserved within gene families, thus increasing the chance of cross hybridizations during chromosomal mapping.

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. (Such data are found, for example, in V. McKusick, Mendelian Inheritance in Man, available on-line through Johns Hopkins University Welch Medical Library). The relationship between genes and disease, mapped to the same chromosomal region, can then be identified through linkage analysis (co-inheritance of physically adjacent genes), described in, e.g., Egeland et al. (1987) *Nature* 325:783-787.

Moreover, differences in the DNA sequences between individuals affected and unaffected with a disease associated with a gene of the invention can be determined. If a mutation is observed in some or all of the affected individuals but not in any unaffected individuals, then the mutation is likely to be the causative agent of the particular disease. Comparison of affected and unaffected individuals generally involves first looking for structural alterations in the chromosomes such as deletions or translocations that are visible from chromosome spreads or detectable using PCR based on that DNA sequence. Ultimately, complete sequencing of genes from several individuals can be performed to confirm the presence of a mutation and to distinguish mutations from polymorphisms.

2. Tissue Typing

The nucleic acid sequences of the present invention can also be used to identify individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identification. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The sequences of the present invention are useful as additional DNA markers for RFLP (described in U.S. Patent 5,272,057).

Furthermore, the sequences of the present invention can be used to provide an alternative technique which determines the actual base-by-base DNA sequence of selected portions of an individual's genome. Thus, the nucleic acid sequences described herein can be used to prepare two PCR primers from the 5' and 3' ends of the sequences. These primers can then be used to amplify an individual's DNA and subsequently sequence it.

Panels of corresponding DNA sequences from individuals, prepared in this manner, can provide unique individual identifications, as each individual will have a unique set of such DNA sequences due to allelic differences. The sequences of the present invention can be used to obtain such identification sequences from individuals and from tissue. The nucleic acid sequences of the invention uniquely represent portions of the human genome. Allelic variation occurs to some degree in the coding regions of these sequences, and to a greater degree in the noncoding regions. It is estimated that allelic variation between individual humans occurs with a frequency of about once

per each 500 bases. Each of the sequences described herein can, to some degree, be used as a standard against which DNA from an individual can be compared for identification purposes. Because greater numbers of polymorphisms occur in the noncoding regions, fewer sequences are necessary to differentiate individuals. For example, the noncoding sequences of SEQ ID NO:1 can comfortably provide positive individual identification with a panel of perhaps 10 to 1,000 primers which each yield a noncoding amplified sequence of 100 bases. If predicted coding sequences, such as those in SEQ ID NO:3 are used, a more appropriate number of primers for positive individual identification would be 500-2,000.

If a panel of reagents from the nucleic acid sequences described herein is used to generate a unique identification database for an individual, those same reagents can later be used to identify tissue from that individual. Using the unique identification database, positive identification of the individual, living or dead, can be made from extremely small tissue samples.

3. Use of Partial Gene Sequences in Forensic Biology

DNA-based identification techniques can also be used in forensic biology. Forensic biology is a scientific field employing genetic typing of biological evidence found at a crime scene as a means for positively identifying, for example, a perpetrator of a crime. To make such an identification, PCR technology can be used to amplify DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, or semen found at a crime scene. The amplified sequence can then be compared to a standard, thereby allowing identification of the origin of the biological sample.

The sequences of the present invention can be used to provide polynucleotide reagents, e.g., PCR primers, targeted to specific loci in the human genome, which can enhance the reliability of DNA-based forensic identifications by, for example, providing another "identification marker" (i.e. another DNA sequence that is unique to a particular individual). As mentioned above, actual base sequence information can be used for identification as an accurate alternative to patterns formed by restriction enzyme generated fragments. Sequences targeted to noncoding regions are particularly appropriate for this use as greater numbers of polymorphisms occur in the noncoding regions, making it easier to differentiate individuals using this technique. Examples of polynucleotide reagents include the nucleic acid sequences of the invention or portions thereof, e.g., fragments derived from noncoding regions having a length of at least 20 or 30 bases.

The nucleic acid sequences described herein can further be used to provide polynucleotide reagents, e.g., labeled or labelable probes which can be used in, for example, an *in situ* hybridization technique, to identify a specific tissue, e.g., brain tissue. This can be very useful in cases where a forensic pathologist is presented with a tissue of unknown origin. Panels of such probes can be used to identify tissue by species and/or by organ type.

C. Predictive Medicine

The present invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trails are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates

to diagnostic assays for determining expression of a polypeptide or nucleic acid of the invention and/or activity of a polypeptide of the invention, in the context of a biological sample (e.g., blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a disease or disorder, or is at risk of developing a disorder, associated with aberrant expression or activity of a polypeptide of the invention. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder associated with aberrant expression or activity of a polypeptide of the invention. For example, mutations in a gene of the invention can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a disorder characterized by or associated with aberrant expression or activity of a polypeptide of the invention.

Another aspect of the invention provides methods for expression of a nucleic acid or polypeptide of the invention or activity of a polypeptide of the invention in an individual to thereby select appropriate therapeutic or prophylactic agents for that individual (referred to herein as "pharmacogenomics"). Pharmacogenomics allows for the selection of agents (e.g., drugs) for therapeutic or prophylactic treatment of an individual based on the genotype of the individual (e.g., the genotype of the individual examined to determine the ability of the individual to respond to a particular agent).

Yet another aspect of the invention pertains to monitoring the influence of agents (e.g., drugs or other compounds) on the expression or activity of a polypeptide of the invention in clinical trials.

These and other agents are described in further detail in the following sections.

1. Diagnostic Assays

An exemplary method for detecting the presence or absence of a polypeptide or nucleic acid of the invention in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of detecting a polypeptide or nucleic acid (e.g., mRNA, genomic DNA) of the invention such that the presence of a polypeptide or nucleic acid of the invention is detected in the biological sample. A preferred agent for detecting mRNA or genomic DNA encoding a polypeptide of the invention is a labeled nucleic acid probe capable of hybridizing to mRNA or genomic DNA encoding a polypeptide of the invention. The nucleic acid probe can be, for example, a full-length cDNA, such as the nucleic acid of SEQ ID NOs:1-22, 34-43, and ___ - ___ or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to a mRNA or genomic DNA encoding a polypeptide of the invention. Other suitable probes for use in the diagnostic assays of the invention are described herein.

A preferred agent for detecting A polypeptide of the invention is an antibody capable of binding to A polypeptide of the invention, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (e.g., Fab or $F(ab')_2$) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as

indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. That is, the detection method of the invention can be used to detect mRNA, protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of A polypeptide of the invention include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of a polypeptide of the invention include introducing into a subject a labeled antibody directed against the polypeptide. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

In one embodiment, the biological sample contains protein molecules from the test subject. Alternatively, the biological sample can contain mRNA molecules from the test subject or genomic DNA molecules from the test subject. A preferred biological sample is a peripheral blood leukocyte sample isolated by conventional means from a subject.

In another embodiment, the methods further involve obtaining a control biological sample from a control

subject, contacting the control sample with a compound or agent capable of detecting a polypeptide of the invention or mRNA or genomic DNA encoding a polypeptide of the invention, such that the presence of the polypeptide or mRNA or genomic DNA encoding the polypeptide is detected in the biological sample, and comparing the presence of the polypeptide or mRNA or genomic DNA encoding the polypeptide in the control sample with the presence of the polypeptide or mRNA or genomic DNA encoding the polypeptide in the test sample.

The invention also encompasses kits for detecting the presence of a polypeptide or nucleic acid of the invention in a biological sample (a test sample). Such kits can be used to determine if a subject is suffering from or is at increased risk of developing a disorder associated with aberrant expression of a polypeptide of the invention (e.g., an immunological disorder). For example, the kit can comprise a labeled compound or agent capable of detecting the polypeptide or mRNA encoding the polypeptide in a biological sample and means for determining the amount of the polypeptide or mRNA in the sample (e.g., an antibody which binds the polypeptide or an oligonucleotide probe which binds to DNA or mRNA encoding the polypeptide). Kits can also include instruction for observing that the tested subject is suffering from or is at risk of developing a disorder associated with aberrant expression of the polypeptide if the amount of the polypeptide or mRNA encoding the polypeptide is above or below a normal level.

For antibody-based kits, the kit can comprise, for example: (1) a first antibody (e.g., attached to a solid support) which binds to a polypeptide of the invention; and, optionally, (2) a second, different antibody which binds to either the polypeptide or the first antibody and is conjugated to a detectable agent.

For oligonucleotide-based kits, the kit can comprise, for example: (1) an oligonucleotide, e.g., a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a polypeptide of the invention or (2) a pair of primers useful for amplifying a nucleic acid molecule encoding a polypeptide of the invention.

The kit can also comprise, e.g., a buffering agent, a preservative, or a protein stabilizing agent. The kit can also comprise components necessary for detecting the detectable agent (e.g., an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample contained. Each component of the kit is usually enclosed within an individual container and all of the various containers are within a single package along with instructions for observing whether the tested subject is suffering from or is at risk of developing a disorder associated with aberrant expression of the polypeptide.

2. Prognostic Assays

The methods described herein can furthermore be utilized as diagnostic or prognostic assays to identify subjects having or at risk of developing a disease or disorder associated with aberrant expression or activity of a polypeptide of the invention. For example, the assays described herein, such as the preceding diagnostic assays or the following assays, can be utilized to identify a subject having or at risk of developing a disorder associated with aberrant expression or activity of a polypeptide of the invention. Alternatively, the prognostic assays can be utilized to identify a subject having or at risk for developing such a disease or disorder. Thus, the present invention provides a method in which a test sample is obtained from a subject and a

polypeptide or nucleic acid (e.g., mRNA, genomic DNA) of the invention is detected, wherein the presence of the polypeptide or nucleic acid is diagnostic for a subject having or at risk of developing a disease or disorder associated with aberrant expression or activity of the polypeptide. As used herein, a "test sample" refers to a biological sample obtained from a subject of interest. For example, a test sample can be a biological fluid (e.g., serum), cell sample, or tissue.

Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) to treat a disease or disorder associated with aberrant expression or activity of a polypeptide of the invention. For example, such methods can be used to determine whether a subject can be effectively treated with a specific agent or class of agents (e.g., agents of a type which decrease activity of the polypeptide). Thus, the present invention provides methods for determining whether a subject can be effectively treated with an agent for a disorder associated with aberrant expression or activity of a polypeptide of the invention in which a test sample is obtained and the polypeptide or nucleic acid encoding the polypeptide is detected (e.g., wherein the presence of the polypeptide or nucleic acid is diagnostic for a subject that can be administered the agent to treat a disorder associated with aberrant expression or activity of the polypeptide).

The methods of the invention can also be used to detect genetic lesions or mutations in a gene of the invention, thereby determining if a subject with the lesioned gene is at risk for a disorder characterized aberrant expression or activity of a polypeptide of the invention.

In preferred embodiments, the methods include detecting, in a sample of cells from the subject, the presence or absence of a genetic lesion or mutation characterized by at least one of an alteration affecting the integrity of a gene encoding the polypeptide of the invention, or the mis-expression of the gene encoding the polypeptide of the invention. For example, such genetic lesions or mutations can be detected by ascertaining the existence of at least one of: 1) a deletion of one or more nucleotides from the gene; 2) an addition of one or more nucleotides to the gene; 3) a substitution of one or more nucleotides of the gene; 4) a chromosomal rearrangement of the gene; 5) an alteration in the level of a messenger RNA transcript of the gene; 6) an aberrant modification of the gene, such as of the methylation pattern of the genomic DNA; 7) the presence of a non-wild type splicing pattern of a messenger RNA transcript of the gene; 8) a non-wild type level of a the protein encoded by the gene; 9) an allelic loss of the gene; and 10) an inappropriate post-translational modification of the protein encoded by the gene. As described herein, there are a large number of assay techniques known in the art which can be used for detecting lesions in a gene.

In certain embodiments, detection of the lesion involves the use of a probe/primer in a polymerase chain reaction (PCR) (*see, e.g.*, U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (*see, e.g.*, Landegran et al. (1988) *Science* 241:1077-1080; and Nakazawa et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:360-364), the latter of which can be particularly useful for detecting point mutations in a gene (*see, e.g.*, Abravaya et al. (1995) *Nucleic Acids Res.* 23:675-682). This method can include the steps of collecting a sample of cells from a patient, isolating nucleic acid (e.g.,

genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to the selected gene under conditions such that hybridization and amplification of the gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

Alternative amplification methods include: self sustained sequence replication (Guatelli et al. (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh, et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi et al. (1988) *Bio/Technology* 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In an alternative embodiment, mutations in a selected gene from a sample cell can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes (*see, e.g.*, U.S. Patent No. 5,498,531) can be used to score for the presence of

specific mutations by development or loss of a ribozyme cleavage site.

In other embodiments, genetic mutations can be identified by hybridizing a sample and control nucleic acids, e.g., DNA or RNA, to high density arrays containing hundreds or thousands of oligonucleotides probes (Cronin et al. (1996) *Human Mutation* 7:244-255; Kozal et al. (1996) *Nature Medicine* 2:753-759). For example, genetic mutations can be identified in two-dimensional arrays containing light-generated DNA probes as described in Cronin et al., *supra*. Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential overlapping probes. This step allows the identification of point mutations. This step is followed by a second hybridization array that allows the characterization of specific mutations by using smaller, specialized probe arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the selected gene and detect mutations by comparing the sequence of the sample nucleic acids with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxim and Gilbert ((1977) *Proc. Natl. Acad. Sci. USA* 74:560) or Sanger ((1977) *Proc. Natl. Acad. Sci. USA* 74:5463). It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the diagnostic assays ((1995) *Bio/Techniques* 19:448), including sequencing by

mass spectrometry (*see, e.g.*, PCT Publication No. WO 94/16101; Cohen et al. (1996) *Adv. Chromatogr.* 36:127-162; and Griffin et al. (1993) *Appl. Biochem. Biotechnol.* 38:147-159).

Other methods for detecting mutations in a selected gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes (Myers et al. (1985) *Science* 230:1242). In general, the technique of "mismatch cleavage" entails providing heteroduplexes formed by hybridizing (labeled) RNA or DNA containing the wild-type sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent which cleaves single-stranded regions of the duplex such as which will exist due to basepair mismatches between the control and sample strands. RNA/DNA duplexes can be treated with RNase to digest mismatched regions, and DNA/DNA hybrids can be treated with S1 nuclease to digest mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. *See, e.g.*, Cotton et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:4397; Saleeba et al. (1992) *Methods Enzymol.* 217:286-295. In a preferred embodiment, the control DNA or RNA can be labeled for detection.

In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in cDNAs obtained from samples of cells. For example, the mutY enzyme of

E. coli cleaves A at G/A mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches (Hsu et al. (1994) *Carcinogenesis* 15:1657-1662). According to an exemplary embodiment, a probe based on a selected sequence, e.g., a wild-type sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the like. *See, e.g.*, U.S. Patent No. 5,459,039.

In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:2766; *see also* Cotton (1993) *Mutat. Res.* 285:125-144; Hayashi (1992) *Genet. Anal. Tech. Appl.* 9:73-79). Single-stranded DNA fragments of sample and control nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, and the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In a preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen et al. (1991) *Trends Genet.* 7:5).

In yet another embodiment, the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing

gradient gel electrophoresis (DGGE) (Myers et al. (1985) *Nature* 313:495). When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a 'GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) *Biophys. Chem.* 265:12753).

Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki et al. (1986) *Nature* 324:163); Saiki et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:6230). Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA.

Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs et al. (1989) *Nucleic Acids Res.* 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent or reduce polymerase extension (Prossner (1993) *Tibtech* 11:238). In addition, it may be desirable to introduce a novel restriction site in the region of the

mutation to create cleavage-based detection (Gasparini et al. (1992) *Mol. Cell Probes* 6:1). It is anticipated that in certain embodiments amplification may also be performed using Taq ligase for amplification (Barany (1991) *Proc. Natl. Acad. Sci. USA* 88:189). In such cases, ligation will occur only if there is a perfect match at the 3' end of the 5' sequence making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits comprising at least one probe nucleic acid or antibody reagent described herein, which may be conveniently used, e.g., in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness involving a gene encoding a polypeptide of the invention.

Furthermore, any cell type or tissue, preferably peripheral blood leukocytes, in which the polypeptide of the invention is expressed may be utilized in the prognostic assays described herein.

3. Pharmacogenomics

Agents, or modulators which have a stimulatory or inhibitory effect on activity or expression of a polypeptide of the invention as identified by a screening assay described herein can be administered to individuals to treat (prophylactically or therapeutically) disorders associated with aberrant activity of the polypeptide. In conjunction with such treatment, the pharmacogenomics (i.e., the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) of the individual may be considered. Differences in metabolism of therapeutics

can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, the pharmacogenomics of the individual permits the selection of effective agents (e.g., drugs) for prophylactic or therapeutic treatments based on a consideration of the individual's genotype. Such pharmacogenomics can further be used to determine appropriate dosages and therapeutic regimens. Accordingly, the activity of a polypeptide of the invention, expression of a nucleic acid of the invention, or mutation content of a gene of the invention in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual.

Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. *See, e.g.*, Linder (1997) *Clin. Chem.* 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body are referred to as "altered drug action." Genetic conditions transmitted as single factors altering the way the body acts on drugs are referred to as "altered drug metabolism". These pharmacogenetic conditions can occur either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase deficiency (G6PD) is a common inherited enzymopathy in which the main clinical complication is haemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of

genetic polymorphisms of drug metabolizing enzymes (e.g., N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, a PM will show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the activity of a polypeptide of the invention, expression of a nucleic acid encoding the polypeptide, or mutation content of a gene encoding the polypeptide in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions

or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a modulator of activity or expression of the polypeptide, such as a modulator identified by one of the exemplary screening assays described herein.

4. Monitoring of Effects During Clinical Trials

Monitoring the influence of agents (e.g., drugs, compounds) on the expression or activity of a polypeptide of the invention (e.g., the ability to modulate aberrant cell proliferation and/or differentiation) can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent, as determined by a screening assay as described herein, to increase gene expression, protein levels or protein activity, can be monitored in clinical trials of subjects exhibiting decreased gene expression, protein levels, or protein activity. Alternatively, the effectiveness of an agent, as determined by a screening assay, to decrease gene expression, protein levels or protein activity, can be monitored in clinical trials of subjects exhibiting increased gene expression, protein levels, or protein activity. In such clinical trials, expression or activity of a polypeptide of the invention and preferably, that of other polypeptide that have been implicated in for example, a cellular proliferation disorder, can be used as a marker of the immune responsiveness of a particular cell.

For example, and not by way of limitation, genes, including those of the invention, that are modulated in cells by treatment with an agent (e.g., compound, drug or small molecule) which modulates activity or expression of a polypeptide of the invention (e.g., as identified in a screening assay described herein) can be identified. Thus, to study the effect of agents on cellular

proliferation disorders, for example, in a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of a gene of the invention and other genes implicated in the disorder. The levels of gene expression (i.e., a gene expression pattern) can be quantified by Northern blot analysis or RT-PCR, as described herein, or alternatively by measuring the amount of protein produced, by one of the methods as described herein, or by measuring the levels of activity of a gene of the invention or other genes. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the cells to the agent. Accordingly, this response state may be determined before, and at various points during, treatment of the individual with the agent.

In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate identified by the screening assays described herein) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of the polypeptide or nucleic acid of the invention in the preadministration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level the of the polypeptide or nucleic acid of the invention in the post-administration samples; (v) comparing the level of the polypeptide or nucleic acid of the invention in the pre-administration sample with the level of the polypeptide or nucleic acid of the invention in the post-administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be

desirable to increase the expression or activity of the polypeptide to higher levels than detected, i.e., to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of the polypeptide to lower levels than detected, i.e., to decrease the effectiveness of the agent.

C. Methods of Treatment

The present invention provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated with aberrant expression or activity of a polypeptide of the invention.

1. Prophylactic Methods

In one aspect, the invention provides a method for preventing in a subject, a disease or condition associated with an aberrant expression or activity of a polypeptide of the invention, by administering to the subject an agent which modulates expression or at least one activity of the polypeptide. Subjects at risk for a disease which is caused or contributed to by aberrant expression or activity of a polypeptide of the invention can be identified by, for example, any or a combination of diagnostic or prognostic assays as described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of the aberrancy, such that a disease or disorder is prevented or, alternatively, delayed in its progression. Depending on the type of aberrancy, for example, an agonist or antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein.

2. Therapeutic Methods

Another aspect of the invention pertains to methods of modulating expression or activity of a polypeptide of the invention for therapeutic purposes. The modulatory method of the invention involves contacting a cell with an agent that modulates one or more of the activities of the polypeptide. An agent that modulates activity can be an agent as described herein, such as a nucleic acid or a protein, a naturally-occurring cognate ligand of the polypeptide, a peptide, a peptidomimetic, or other small molecule. In one embodiment, the agent stimulates one or more of the biological activities of the polypeptide. Examples of such stimulatory agents include the active polypeptide of the invention and a nucleic acid molecule encoding the polypeptide of the invention that has been introduced into the cell. In another embodiment, the agent inhibits one or more of the biological activities of the polypeptide of the invention. Examples of such inhibitory agents include antisense nucleic acid molecules and antibodies. These modulatory methods can be performed *in vitro* (e.g., by culturing the cell with the agent) or, alternatively, *in vivo* (e.g, by administering the agent to a subject). As such, the present invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant expression or activity a polypeptide of the invention. In one embodiment, the method involves administering an agent (e.g., an agent identified by a screening assay described herein), or combination of agents that modulates (e.g., upregulates or downregulates) expression or activity. In another embodiment, the method involves administering a polypeptide of the invention or a nucleic acid molecule of the invention as therapy to compensate for reduced or aberrant expression or activity of the polypeptide.

Stimulation of activity is desirable in situations in which activity or expression is abnormally low downregulated and/or in which increased activity is likely to have a beneficial effect. Conversely, inhibition of activity is desirable in situations in which activity or expression is abnormally high or upregulated and/or in which decreased activity is likely to have a beneficial effect.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application are hereby incorporated by reference.

EXAMPLES

TANGO 180, TANGO 181, TANGO 182, TANGO 183, TANGO 184, TANGO 185, TANGO 186, TANGO 188, TANGO 189 and TANGO 187, were identified in a human prostate epithelial cell library. TANGO 215 was identified in a human prostate stromal cell library.

TANGO 180, TANGO 181, TANGO 182, TANGO 183, TANGO 184, TANGO 185, TANGO 186, TANGO 188, TANGO 189, TANGO 215, and TANGO 187 were identified by first analyzing clones present in the two libraries to identify EST sequences which potentially encode a signal peptide having at least 15 amino acids. Selected clones which include an EST sequence that appeared to encode a signal peptide having at least 15 amino acids were used to assemble additional EST sequences to form potential full-length gene sequences. The assembled full-length gene sequences were then used to identify actual full-length clones in the two libraries.

Deposit of Clones

Clones containing cDNA molecules encoding TANGO 180, TANGO 181, TANGO 182, TANGO 183, TANGO 184, TANGO 185,

TANGO 186, TANGO 188, TANGO 189, TANGO 215 and TANGO 187 were deposited with the American Type Culture Collection (Manassas, VA) as composite deposits.

Clones encoding TANGO 180, TANGO 181, TANGO 182 and TANGO 183, and TANGO 184 were deposited on September 25, 1998 with the American Type Culture Collection under accession number ATCC 98901, from which each clone comprising a particular cDNA clone is obtainable. This deposit is a mixture of five strains, each carrying one recombinant plasmid harboring a particular cDNA clone. To distinguish the strains and isolate a strain harboring a particular cDNA clone, one can first streak out an aliquot of the mixture to single colonies on nutrient medium (e.g., LB plates) supplemented with 100μg/ml ampicillin, grow single colonies, and then extract the plasmid DNA using a standard minipreparation procedure. Next, one can digest a sample of the DNA minipreparation with a combination of the restriction enzymes *Sal* I and *Not* I and resolve the resultant products on a 0.8% agarose gel using standard DNA electrophoresis conditions. The digest will liberate fragments as follows:

TANGO 180 (EpT180)	1.2 kb and 2.7 kb
TANGO 181 (EpT181)	4.5 kb and 2.7 kb
TANGO 182 (EpT182)	two 2.7 kb fragments
TANGO 183 (EpT183)	1.6 kb and 2.7 kb
TANGO 184 (EpT184)	4.5 kb

The identity of the strains can be inferred from the fragments liberated.

Clones encoding TANGO 185, TANGO 186, TANGO 187, TANGO 188 and TANGO 189 (splice variant 1) were deposited on September 25, 1998 with the American Type Culture Collection under accession number ATCC 98900, from which each stain comprising a particular cDNA clone is obtainable. The deposit is a mixture of five strains,

each carrying one recombinant plasmid harboring a particular cDNA clone. To distinguish the strains and isolate a strain harboring a particular cDNA clone, one can first streak out an aliquot of the mixture to single colonies on nutrient medium (e.g., LB plates) supplemented with 100μg/ml ampicillin, grow single colonies, and then extract the plasmid DNA using a standard minipreparation procedure. Next, one can digest a sample of the DNA minipreparation with a combination of the restriction enzymes *Sal* I and *Not* I and resolve the resultant products on a 0.8% agarose gel using standard DNA electrophoresis conditions. The digest will liberate one vector fragment of 2.7 kb common to all strains, and one insert-specific fragment as follows:

TANGO 185 (EpT185)	2.1 kb
TANGO 186 (EpT186)	3.7 kb
TANGO 187 (EpT187)	2.6 kb
TANGO 188 (EpT188)	2.0 kb
TANGO 189 (EpT189sv1)	1.3 kb

The identity of the strains can be inferred from the fragments liberated.

A clone encoding TANGO 215 and four other clones were deposited on September 25, 1998 with the American Type Culture Collection under accession number ATCC 98899, from which the srrain comprising the TANGO 215 cDNA clone is obtainable. To distinguish the strains and isolate a strain harboring the TANGO 215 cDNA clone, one can first streak out an aliquot of the mixture to single colonies on nutrient medium (e.g., LB plates) supplemented with 100μg/ml ampicillin, grow single colonies, and then extract the plasmid DNA using a standard minipreparation procedure. Next, one can digest a sample of the DNA minipreparation with a combination of the restriction enzymes *Sal* I and *Not* I and resolve the resultant

products on a 0.8% agarose gel using standard DNA electrophoresis conditions.

The digest will liberate one vector fragment of 2.7 kb common to all strains, and one insert-specific fragment as follows:

TANGO 215 (EpT215) 2.8 kb

The identity of the strain harboring the TANGO 215 cDNA clone can be inferred from the fragments liberated.

Equivalents

The contents of all references, patents and published patent applications cited throughout this application are hereby incorporated by reference. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed is:

1. An isolated nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule comprising a nucleotide sequence which is at least 55% identical to the nucleotide sequence of any of SEQ ID NOs:1-22, 34-43, and ___ - ___, the cDNA insert of a plasmid deposited with the ATCC as any of Accession Numbers 98899, 98900, and 98901, or a complement thereof;

b) a nucleic acid molecule comprising a fragment of at least 300 nucleotides of the nucleotide sequence of any of SEQ ID NOs:1-22, 34-43, and ___ - ___, the cDNA insert of a plasmid deposited with the ATCC as any of Accession Numbers 98899, 98900, and 98901, or a complement thereof;

c) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of any of SEQ ID Nos:23-33, 54-63, and ___ - ___ or an amino acid sequence encoded by the cDNA insert of a plasmid deposited with the ATCC as any of Accession Numbers 98899, 98900, and 98901;

d) a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of any of SEQ ID NOs:23-33, 54-63, and ___ - ___ wherein the fragment comprises at least 15 contiguous amino acids of any of SEQ ID NOs:23-33, 54-63, and ___ - ___ or the polypeptide encoded by the cDNA insert of a plasmid deposited with the ATCC as any of Accession Numbers 98899, 98900, and 98901; and

e) a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of any of SEQ ID NOs:23-33, 54-63, and __ - ___ or an amino acid sequence encoded by the cDNA insert of a plasmid deposited with ATCC as any of Accession Numbers 98899, 98900, and 98901, wherein the

nucleic acid molecule hybridizes to a nucleic acid molecule comprising any of SEQ ID Nos:1-22, 34-43, and ___ - ___ or a complement thereof under stringent conditions.

2. The isolated nucleic acid molecule of claim 1, which is selected from the group consisting of:

a) a nucleic acid molecule comprising the nucleotide sequence of any of SEQ ID NO:1-22 and 34-43, the cDNA insert of a plasmid deposited with the ATCC as any of Accession Numbers 98899, 98900, and 98901, or a complement thereof; and

b) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of any of SEQ ID Nos:23-33, 54-63, and ___ - ___ or an amino acid sequence encoded by the cDNA insert of a plasmid deposited with the ATCC as any of Accession Numbers 98899, 98900, and 98901.

3. The nucleic acid molecule of claim 1 further comprising vector nucleic acid sequences.

4. The nucleic acid molecule of claim 1 further comprising nucleic acid sequences encoding a heterologous polypeptide.

5. A host cell which contains the nucleic acid molecule of claim 1.

6. The host cell of claim 5 which is a mammalian host cell.

7. A non-human mammalian host cell containing the nucleic acid molecule of
claim 1.

8. An isolated polypeptide selected from the group consisting of:

a) a fragment of a polypeptide comprising the amino acid sequence of any of SEQ ID Nos:23-33, 54-63, and __ - ___, wherein the fragment comprises at least 15 contiguous amino acids of any of SEQ ID Nos:23-33 and 54-63, and ___ - ___;

b) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of any of SEQ ID Nos:23-33, 54-63, and ___ - ___ or an amino acid sequence encoded by the cDNA insert of a plasmid deposited with the ATCC as any of Accession Numbers 98899, 98900, and 98901, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising any of SEQ ID Nos:1-22, 34-43, and ___ - ___ or a complement thereof under stringent conditions; and

c) a polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 55% identical to a nucleic acid comprising the nucleotide sequence of any of SEQ ID Nos:1-22, 34-43, and ___ - ___ or a complement thereof.

9. The isolated polypeptide of claim 8 comprising the amino acid sequence of any of SEQ ID Nos:23-33, 54-63, and ___ - ___ or an amino acid sequence encoded by the cDNA insert of a plasmid deposited with the ATCC as any of Accession Numbers 98899, 98900, and 98901.

10. The polypeptide of claim 8 further comprising heterologous amino acid sequences.

11. An antibody which selectively binds to a polypeptide of claim 8.

12. A method for producing a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of any of SEQ ID Nos:23-33, 54-63, and ___ - ___ or an amino acid sequence encoded by the cDNA insert of a plasmid deposited with the ATCC as any of Accession Numbers 98899, 98900, and 98901;

b) a polypeptide comprising a fragment of the amino acid sequence of any of SEQ ID Nos:23-33, 54-63, and ___ - ___ or an amino acid sequence encoded by the cDNA insert of a plasmid deposited with the ATCC as any of Accession Numbers 98899, 98900, and 98901, wherein the fragment comprises at least 15 contiguous amino acids of any of SEQ ID Nos:23-33, 54-63, and ___ - ___ or an amino acid sequence encoded by the cDNA insert of a plasmid deposited with the ATCC as any of Accession Numbers 98899, 98900, and 98901; and

c) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of any of SEQ ID Nos:23-33, 54-63, and ___ - ___ or an amino acid sequence encoded by the cDNA insert of a plasmid deposited with the ATCC as any of Accession Numbers 98899, 98900, and 98901, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising the nucleotide sequence of any of SEQ ID Nos:1-22, 54-63, and ___ - ___ or a complement thereof under stringent conditions;

comprising culturing the host cell of claim 5 under conditions in which the nucleic acid molecule is expressed.

13. A method for detecting the presence of a polypeptide of claim 8 in a sample, comprising:

a) contacting the sample with a compound which selectively binds to a polypeptide of claim 8; and

b) determining whether the compound binds to the polypeptide in the sample.

14. The method of claim 13, wherein the compound which binds to the polypeptide is an antibody.

15. A kit comprising a compound which selectively binds to a polypeptide of claim 8 and instructions for use.

16. A method for detecting the presence of a nucleic acid molecule of claim 1 in a sample, comprising the steps of:

a) contacting the sample with a nucleic acid probe or primer which selectively hybridizes to the nucleic acid molecule; and

b) determining whether the nucleic acid probe or primer binds to a nucleic acid molecule in the sample.

17. The method of claim 16, wherein the sample comprises mRNA molecules and is contacted with a nucleic acid probe.

18. A kit comprising a compound which selectively hybridizes to a nucleic acid molecule of claim 1 and instructions for use.

19. A method for identifying a compound which binds to a polypeptide of claim 8 comprising the steps of:

a) contacting a polypeptide, or a cell expressing a polypeptide of claim 8 with a test compound; and

b) determining whether the polypeptide binds to the test compound.

20. The method of claim 19, wherein the binding of the test compound to the polypeptide is detected by a method selected from the group consisting of:

a) detection of binding by direct detecting of the binding of the test compound to the polypeptide binding; and

b) detection of binding using a competition binding assay.

21. A method for modulating the activity of a polypeptide of claim 8 comprising contacting a polypeptide or a cell expressing a polypeptide of claim 8 with a compound which binds to the polypeptide in a sufficient concentration to modulate the activity of the polypeptide.

22. A method for identifying a compound which modulates the activity of a polypeptide of claim 8, comprising:

a) contacting a polypeptide of claim 8 with a test compound; and

b) determining the effect of the test compound on the activity of the polypeptide to thereby identify a compound which modulates the activity of the polypeptide.

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GTCGACCCACGCGTCCGCGTGGATATGGAGCTGGCTGCTGCCAAGTCCGGGGCCCGCGCCGCTGCCTAGCGCGTCCTGG 79

                                                                  M  A  L  L    4
GGACTCTGTGGGGACGCGCCCCGCGCCGCGGCTCGGGGACCCGTAGAGCCCGGCGCTGCGCGC ATG GCC CTG CTC  154

 S  R  P  A  L  T  L  L  L  L  L  M  A  A  V  V  R  C  Q  E   24
TCG CGC CCC GCG CTC ACC CTC CTG CTC CTC CTC ATG GCC GCT GTT GTC AGG TGC CAG GAG  214

 Q  A  Q  T  T  D  W  R  A  T  L  K  T  I  R  N  G  V  H  K   44
CAG GCC CAG ACC ACC GAC TGG AGA GCC ACC CTG AAG ACC ATC CGG AAC GGC GTT CAT AAG  274

 I  D  T  Y  L  N  A  A  L  D  L  L  G  G  E  D  G  L  C  Q   64
ATA GAC ACG TAC CTG AAC GCC GCC TTG GAC CTC CTG GGA GGC GAG GAC GGT CTC TGC CAG  334

 Y  K  C  S  D  G  S  K  P  F  P  R  Y  G  Y  K  P  S  P  P   84
TAT AAA TGC AGT GAC GGA TCT AAG CCT TTC CCA CGT TAT GGT TAT AAA CCC TCC CCA CCG  394

 N  G  C  G  S  P  L  F  G  V  H  L  N  I  G  I  P  S  L  T  104
AAT GGA TGT GGC TCT CCA CTG TTT GGT GTT CAT CTT AAC ATT GGT ATC CCT TCC CTG ACA  454

 K  C  C  N  Q  H  D  R  C  Y  E  T  C  G  K  S  K  N  D  C  124
AAG TGT TGC AAC CAA CAC GAC AGG TGC TAT GAG ACC TGT GGC AAA AGC AAG AAT GAC TGT  514

 D  E  E  F  Q  Y  C  L  S  K  I  C  R  D  V  Q  K  T  L  G  144
GAT GAA GAA TTC CAG TAT TGC CTC TCC AAG ATC TGC CGA GAT GTA CAG AAA ACA CTA GGA  574

 L  T  Q  H  V  Q  A  C  E  T  T  V  E  L  L  F  D  S  V  I  164
CTA ACT CAG CAT GTT CAG GCA TGT GAA ACA ACA GTG GAG CTC TTG TTT GAC AGT GTT ATA  634

 H  L  G  C  K  P  Y  L  D  S  Q  R  A  A  C  R  C  H  Y  E  184
CAT TTA GGT TGT AAA CCA TAT CTG GAC AGC CAA CGA GCC GCA TGC AGG TGT CAT TAT GAA  694

 E  K  T  D  L  *                                               190
GAA AAA ACT GAT CTT TAA                                         712

AGGAGATGCCGACAGCTAGTGACAGATGAAGATGGAAGAACATACCTTTGACAAATAACTAATGTTTTTACAACATAAA 791

ACTGTCTTATTTTTGTGAAAGGATTATTTTGAGACCTTAAAATAATTTATATCTTGATGTTAAAACCTCAAAGCAAAAA 870

AAGTGAGGGAGATAGTGAGGGGAGGGCACGCTTGTCTTCTCAGGTATCTTCCCCAGCATTGCTCCCTTACTTAGTATGC 949

CAAATGTCTTGACCAATATCAAAAACAAGTGCTTGTTTAGCGGAGAATTTTGAAAAGAGGAATATATAACTCAATTTTC 1028

ACAACCACATTTACCAAAAAAAAGAGATCAAATATAAAATTCATCATAATGTCTGTTCAACATTATCTTATTTGGAAAAT 1107

GGGGAAATTATCACTTACAAGTATTTGTTTACTATGAAATTTTAAATACACATTTATGCCTAGAAAAAAAAAAAAAAAA 1186

AAAAAAAGGGCGGCCGC                                                                 1203
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Fig

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GTCGACCCACGCGTCCGGGCCGGGGTCCTGAGCCGGAGCCGGAGCGCGCGCCGCTGCCCAGCCCCGCCGCGCCGGCCCC 79

      M  V  T  P  R  P  A  P  A  R  G  P  A  L  L  L  L  L          18
GCAG ATG GTG ACT CCG CGG CCC GCG CCC GCC CGG GGC CCC GCG CTC CTC CTC CTC CTG      137

 L  L  A  T  A  R  G  Q  E  Q  D  Q  T  T  D  W  R  A  T  L     38
CTG CTG GCC ACT GCG CGC GGG CAG GAA CAG GAC CAG ACC ACC GAC TGG AGG GCC ACC CTC  197

 K  T  I  R  N  G  I  H  K  I  D  T  Y  L  N  A  A  L  D  L     58
AAG ACC ATC CGC AAC GGC ATC CAC AAG ATA GAC ACG TAC CTC AAC GCC GCG CTG GAC CTG  257

 L  G  G  E  D  G  L  C  Q  Y  K  C  S  D  G  S  K  P  V  P     78
CTG GGC GGG GAG GAC GGG CTC TGC CAG TAC AAG TGC AGC GAC GGA TCG AAG CCT GTT CCA  317

 R  Y  G  Y  K  P  S  P  P  N  G  C  G  S  P  L  F  G  V  H     98
CGC TAT GGA TAT AAA CCA TCT CCA CCA AAT GGC TGT GGC TCT CCA CTG TTT GGC GTT CAT  377

 L  N  I  G  I  P  S  L  T  K  C  C  N  Q  H  D  R  C  Y  E    118
CTG AAC ATA GGT ATC CCT TCC CTG ACC AAG TGC TGC AAC CAG CAC GAC AGA TGC TAT GAG  437

 T  C  G  K  S  K  N  D  C  D  E  E  F  Q  Y  C  L  S  K  I    138
ACC TGC GGG AAA AGC AAG AAC GAC TGT GAC GAG GAG TTC CAG TAC TGC CTC TCC AAG ATC  497

 C  R  D  V  Q  K  T  L  G  L  S  Q  N  V  Q  A  C  E  T  T    158
TGC AGA GAC GTG CAG AAG ACG CTC GGA CTA TCT CAG AAC GTC CAG GCA TGT GAG ACA ACG  557

 V  E  L  L  F  D  S  V  I  H  L  G  C  K  P  Y  L  D  S  Q    178
GTG GAG CTC CTC TTT GAC AGC GTC ATC CAT TTA GGC TGC AAG CCA TAC CTG GAC AGC CAG  617

 R  A  A  C  W  C  R  Y  E  E  K  T  D  L  *                  193
CGG GCT GCA TGC TGG TGT CGT TAT GAA GAA AAA ACA GAT CTA TAA                      662

AGACCCTGACTGCTGGAGAGCAGGCGAGAATGGAGGATCATCCTTGCCAAAGATCGGATGCTTTAACAGCCTAATGTTG  741

CCTTAGTTTTGTGTCGATGGGTCATTTTGAGACCTTTCTATACTGTGTCTTTTTTTAGAACCTCAAAGTGAAAACGGTG  820

GGGGGCCAGGCAGAAACAGAGGGAGAGCATGCTTGGGATGGGGAGCGAGCAGGACATCCAAGAGCATGCCTTCCTGAGA  899

CTCGCTGTCTTGGTGGCTCCCCCAAACTGGGAAGAAAAGCTTAAGCTCGTGTGACTTGGTGTTCATAGTTGTACTTAAC  978

AATAAAAATGAAAGCAAATGTAAAATTCATTGTAAGGACTTTTCAGCATTATTTTATTTTGAAATACAGGCCAATCTTC 1057

CCTTAGAACTATTATTTATTTTGAAATTTCAGATGTACATTTATACCTGGAAAAACTATTAATTCTCCATTTTTATTAT 1136

ACATAATGTGTTGTTTCTCTGAAGCCCACTAAGATAGGTATAAATATGTTACTCAAAACTACACGGTTTCCAAATGTGC 1215

ATCTCTTGTACAGTTGGAATCACGGTTGGTACTTCTCTGGAGAGACGCCCCAGGACATCTGAGTGTTGGGATGTGCACA 1294

GAATTCAGAAGCCCAGCTTCCTGTCTCACAAACCGCTTAGAGTGAATGTCCTTCCTCTCCTGCTGTGAGCTCTAGGAAT 1373

GACGGGTTTAACGGGCCAAGCCGAGCTCTGAATCAGTGCGCTATCTGCTGCTGAGGTTGTGGTTACTCCCTCATCCCCG 1452

TTTTCCATCTTCTATCCTGGAGTAGTGTTAAAAGTCTGACATTTTCTAATGGAGGTCTTAATAAAAGCTATTTACTTCT 1531

TGGTAAAAAAAAAAAAAAAAAAAAAAAAAAAAGGGCGGCCG 1570
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FIG 2

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ACCACCCGTCCGCCCACGCGTCCGGTCGCGTGCTGAGGGGTGTGACGGTTTTCTTGCTCGTGGGCTCGGACGAGTACGG 79

                                        M  A  Q  L  G  A  V  V  A  V      10
AGCGCCTGCAGGGACAGCCTGGATAAAGGCTCACTG ATG GCT CAG TTG GGA GCA GTT GTG GCT GTG      145

 A  S  S  F  F  C  A  S  L  F  S  A  V  H  K  I  E  E  G  H      30
GCT TCC AGT TTC TTT TGT GCA TCT CTC TTC TCA GCT GTG CAC AAG ATA GAA GAG GGA CAT   205

 I  G  V  Y  Y  R  G  G  A  L  L  T  S  T  S  G  P  G  F  H      50
ATT GGG GTA TAT TAC AGA GGC GGT GCC CTG CTG ACT TCG ACC AGC GGC CCT GGT TTC CAT   265

 L  M  L  P  F  I  T  S  Y  K  S  V  Q  T  T  L  Q  T  D  E      70
CTC ATG CTC CCT TTC ATC ACA TCA TAT AAG TCT GTG CAG ACC ACA CTC CAG ACA GAT GAG   325

 V  K  N  V  P  C  G  T  S  G  G  V  M  I  Y  F  D  R  I  E      90
GTG AAG AAT GTA CCT TGT GGG ACT AGT GGT GGT GTG ATG ATC TAC TTT GAC AGA ATT GAA   385

 V  V  N  F  L  V  P  N  A  V  Y  D  I  V  K  N  Y  T  A  D     110
GTG GTG AAC TTC CTG GTC CCG AAC GCA GTG TAT GAT ATA GTG AAG AAC TAT ACT GCT GAC   445

 Y  D  K  A  L  I  F  N  K  I  H  H  E  L  N  Q  F  C  S  V     130
TAT GAC AAG GCC CTC ATC TTC AAC AAG ATC CAC CAC GAA CTG AAC CAG TTC TGC AGT GTG   505

 H  T  L  Q  E  V  Y  I  E  L  F  D  Q  I  D  E  N  L  K  L     150
CAC ACG CTT CAA GAG GTC TAC ATT GAG CTG TTT GAT CAG ATT GAT GAA AAT CTC AAA CTG   565

 A  L  Q  Q  D  L  T  S  M  A  P  G  L  V  I  Q  A  V  R  V     170
GCT TTG CAA CAG GAC CTG ACC TCC ATG GCC CCT GGG CTG GTC ATT CAA GCT GTG CGG GTA   625

 T  K  P  N  I  P  E  A  I  R  R  N  Y  E  L  M  E  S  E  K     190
ACA AAG CCC AAC ATA CCA GAG GCA ATC CGC AGA AAC TAC GAG TTG ATG GAA AGT GAG AAG   685

 T  K  L  L  I  A  A  Q  K  Q  K  V  V  E  K  E  A  E  T  E     210
ACA AAG CTT CTC ATT GCC GCC CAG AAA CAG AAG GTG GTG GAA AAG GAA GCA GAG ACA GAG   745

 R  K  K  A  L  I  E  A  E  K  V  A  Q  V  A  E  I  T  Y  G     230
CGG AAG AAG GCG CTC ATT GAG GCA GAA AAA GTG GCC CAG GTG GCT GAG ATC ACC TAC GGG   805

 Q  K  V  M  E  K  E  T  E  K  K  I  S  E  I  E  D  A  A  F     250
CAG AAG GTG ATG GAG AAG GAG ACT GAG AAG AAG ATT TCA GAA ATT GAA GAT GCT GCA TTT   865

 L  A  R  E  K  A  K  A  D  A  E  C  Y  T  A  M  K  I  A  E     270
CTG GCC CGG GAG AAG GCA AAG GCA GAT GCT GAG TGC TAC ACT GCT ATG AAA ATA GCC GAA   925

 A  N  K  L  K  L  T  P  E  Y  L  Q  L  M  K  Y  K  A  I  A     290
GCC AAT AAG CTG AAG CTA ACC CCT GAA TAT CTG CAG CTG ATG AAG TAC AAG GCC ATT GCT   985

 S  N  S  K  I  Y  F  G  K  D  I  P  N  M  F  M  D  S  A  G     310
TCC AAC AGC AAG ATT TAC TTT GGC AAA GAC ATT CCT AAC ATG TTC ATG GAC TCT GCG GGC  1045

 S  V  S  K  Q  F  E  G  L  A  D  K  L  S  F  G  L  E  D  E     330
AGT GTG AGC AAG CAG TTT GAG GGG CTA GCT GAC AAG CTA AGC TTT GGC TTA GAA GAT GAA  1105

 P  L  E  T  A  T  K  E  N  *                                    340
CCC TTG GAG ACG GCC ACT AAG GAG AAT TGA                          1135
```

Fig 3 (1 of 3)

AAAAAACTTGATATGACTGCAAATGATACTTAAGCAGATCTTTATTTTTTAAGATGAATCAGAATGTTCCTCCCTCCCC 1214

GACTACCTTCTCTGACTGTCTTCCAGTTACTGTGGTGAAAAAGAAGAAATGAACTTAAATCCACTCCCTTTCTAGGGAA 1293

AGGAGGGTGGGGACTGATGATGGGGGGTTTTATTTCAGGTAAGCAGTTTATATGACTTCCAATAAGATTTGTAAATCAT 1372

GGGCTTGACCTTTGACCTCTAGACACTAATTTTATCCTTTGAGGCTGGCTTAATTAGGGATGCTGTCATTAAGGAGAGG 1451

GAGAAATGTAGAGTGTTACCTCCAACTCATTTGATTTCCCTTACTTGGGAAAATGCAGTCCAGTGTTCTCACCTCTGCC 1530

TCCAAGGTAGGAGATGTCTGTGGGTGAGGCTCAGCAACTGAGCAAATATGTGCCTGTGAGTTTGCCAGTAGAGCTGTGA 1609

AGAAACAGCTGCAGAGAACATTTGACCTTCCTGGCATTCTTGTCTGCATGTGTGTGAGTTATTTTAGAGGTGTGCTTTC 1688

TTGAGCCCTCATAAGGAAGTACTGGTGCTAGGTTTTGCAAGATTTTGTATACACTTTGCTCCTTGCCCTAGGGCTCAGA 1767

GTGGTGGTTTCTGACTACATTTCTAGAGTCAGAGCTTGATCACCACAACTCAATTATTTCGGCATCTTTTCACCTATGC 1846

TGTGATTTGTTTTTTTTTTTTCTTCTCAAAAATTCTGTTCATTGGTTCCACTCAGCATCAAGAAGACAGGGACAAACAA 1925

CTCAAGTGTCTTAACAGCTGCTGGAGTGGGATCCTTGTTATCTCTTAGCCACTGCAGGACCTGCCTGACAGGTTATGTG 2004

TGCACCTCGAGATGAAGTGTCTTTCTATTATTGTAGAGATTCTGTAGTGAAGAGGTCTGACACCATGTGTGGAGGAGGA 2083

GGAACGATCAGTCAAGAGATGTCCTGGTCTTAATGCCTGTGGCTTGTGCTGGGAGTGGGTCTGACTTAGTGATAAAAGG 2162

ACTCTATTCACTAAGTAGCCTGTGTTTTTAAATCCAGGGCTGCAGGCAGCAACGCAAGTCAGGCTGAACATTCAGTCTC 2241

CAGAGACAGCTGTGTGGAGCAAATCAGAGTTCATGCCCAAGTCCCCAGGTTGGAATGGCTGTGCCAAAATCCATTCAAA 2320

GGGTTTTCTTTTTCATTACTAGGTCAGAACATTTTGAGTCACCTTGGGAGATTCAGGATGGGGAGAGCAAATTTGAACA 2399

AAAGGTTTTTCTTATATCCTGAGATTGAGGGGTAGGGGGTGTCCAACCTGTATAGCCCATGGGTTGTGTCTAGAATTAA 2478

GTGGAGGGCAGCTATCTGGAGTTAACTTGCAAGCATATTGGTGCCCTCCATGACCACCTCTGGCTTAGGACTTGGCCCT 2557

GTTATGAGCTGACCCCCACCCCCCACCCCCCACCCCCCCCCCCCGCCAACTCCTATACCTATCTTCCCTAGGTGAATCTG 2636

TGAATGGTCCTTTCTGGCAGCAATCCCTGCCTTCTTTTTGGGCCCATGCCCAGACTTCTGGTTTAAGGAATGGTCCCAG 2715

AGCTTGGGCCAGCTTGCTCAGAAGTTTTGGGAGCATTGAGCCTGCCTAGAAAGATACAGTGTTAGCTCCCCTTACTTCA 2794

AAGTTGCCCTTCTCTGTTCWGACTCCTGGGACTTCTGGTCCTGGGCACACTTTTTGCAGGCAACAAAATGTGCCTGGGA 2873

GTGATGGATTTTAATGTGCTCCAGAGTCCTTTCAGAAGGTGGTCATTTCCCTTGGCCGGGCGCGGTGGCTCACACCTGT 2952

AATCCCAGCACTTTGGGAGGCCAAGGCAGGCGGATCACCTGAGGTTAGGAGTTCGAGACCACCCTGGCCAACATGCGAA 3031

ACCCCATCTCTACGAAAAATAGAAATATTAGCCGGGCATGGTGTCAGGCACCTGTAATCCCAGCTACTTGGGAGGCTGA 3110

GGCAGGAGAATTGCTTGAACTCGGGAGGCAGAGGTTGCAGTGAGCCAAGATCATGCCATCCCACTCTAGCTTGGGCAAT 3189

AGAGCAAGGCTCCGTCTCAAGAAAAGAAGGTCATTTCCCAAGACTAGCATAGGGAGTATCCATTTAAAATACATTCATC 3268

TTCCTCCCATTTCCGTGCTATTAATCACTTGTTAGAGCAACATGACAATGCCCAGCATCCCACTTCCCGAAAATGTCTA 3347

CTCCTTCTACTCTGAGCTCTTGTTGCCTAGACCTCAGAAAACACCAATTCACCACAGTAGAACCGGGAGCAGGGATAGC 3426

TCAGCTTCTCTGAATAGCACACTTTGCTCAGGTCTTAACTTGAGGGCCTCTCCGGTACTAACATCCTGCGATAGCTTGT 3505

FIG 3 (2 OF 5)

CCCATGAGCACAGAAGAGCCTCAGTAGAGTCAAGTCCTGCTGCAGCTGCCCCACCCCAAGTTTCTATCATTTCCTCTTT 3584

AAACAAAAAATATGTTATCCTACACATTAGTGTCAATCCAATGGTTGTCTCTTATCTGCTAAATAGCAAAATCATGAAA 3663

ATCAGCTGTTTTATTTGCATAGGCAACTAACCTGTCTGTGTAACTTTGTTTTTATTTTAACTCTTACTAGAAAATCTAA 3742

TCTTAAAACATTTGAATTCTAAACATGTAAAATGTGACAGCCTGCAATTTTGTAGACAGTGAAGTAATGGCTGCTATTT 3821

ATAAACAGTTACTTATTTTGATAGATGTTCCATTTATCAAAATAAGTAACTGTTTATAAAATTCAGTTTTTGTAGGGTT 3900

TTCCAAGGAAAAATCACCTTGGTTGAATGTTTCTCACTCATTAAACTTTGCAGAAGTGATTCATATTCAGTACTGTTTT 3979

TAATCACTTTTTAAAATATAAGGACCGAATGCAAGGAAACCAAAGTTTATTAATAATTTTTATATAACTAAAATAAAAT 4058

AGATGTGGAGGGATCTGTGATCATATAAAAAGGGAGGGTTACTGAAAGAATTTTAGCAATATATTGATTCAGGAAAAGG 4137

AGCTGTTTTATAAATGATCATTCACTGTTCCTATGGTTCTATGTATCTTTCAAACCGATACCTTTACTATTTAAAGAGC 4216

GTAAATAGTGAAAGTAAGATGGTCATACTTACTGACTTTATCTATTTAAGTTTGATGGAGATAAACTATATCTTGGCTA 4295

GTGGCTACTGTGTCTGTGAATGTAACCAGTACTTCTTTAAGCTCTATTCAGTAGGGTTCCAGCCACTGCTTTTTTGTTG 4374

TTTCTAGCCACTGTTTTTTTTTTCTTGTTTCCTTATAAAACAGGTAATAACCAAAAAAAAAAAAAAAAAGGGCGGCCG 4451

Fig 3 (3 of 5)

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GTCGACCCACGCGTCCGCGGACGCGTGGGCGCGGACTGATGGCGTCATCGAAGCGACTGGCCCGGAAGGAAGTAGGGTG 79

CTGAGGGGTGTGGCGGTTTCTACGGTTGCACGGGGGTTCGGCTGTGTACGGAGCGCCTGGAGGGACAGCCTGGATACAG 158

          M   A   Q   L   G   A   V   V   A   V   A   S   S   F   F   C   A      17
GTTCACTG ATG GCT CAG TTG GGA GCT GTT GTG GCC GTG GCT TCC AGT TTC TTT TGT GCA      217

 S   L   F   S   A   V   H   K   I   E   E   G   H   I   G   V   Y   Y   R   G   37
TCT CTC TTC TCA GCT GTG CAC AAG ATA GAA GAG GGA CAT ATT GGA GTA TAT TAC AGA GGT  277

 G   A   L   L   T   S   T   S   G   P   G   F   H   L   M   L   P   F   I   T  57
GGT GCC CTG CTG ACC TCC ACC AGT GGC CCG GGT TTC CAT CTC ATG CTC CCG TTC ATC ACA  337

 S   Y   K   S   V   Q   T   T   L   Q   T   D   E   V   K   N   V   P   C   G   77
TCC TAT AAG TCT GTA CAG ACC ACT CTC CAA ACT GAT GAA GTG AAG AAC GTA CCA TGT GGA  397

 T   S   G   G   V   M   I   Y   F   D   R   I   E   V   V   N   F   L   V   P   97
ACC AGT GGT GGT GTG ATG ATC TAC TTT GAC AGA ATT GAA GTG GTG AAC TTC CTG GTC CCA  457

 N   A   V   Y   D   I   V   K   N   Y   T   A   D   Y   D   K   A   L   I   F  117
AAT GCA GTG TAT GAT ATA GTG AAG AAC TAT ACT GCA GAC TAT GAC AAG GCC CTC ATC TTC  517

 N   K   I   H   H   E   L   N   Q   F   C   S   V   H   T   L   Q   E   V   Y  137
AAC AAG ATC CAT CAT GAG CTT AAC CAG TTC TGC AGC GTT CAT ACT CTT CAG GAA GTC TAT  577

 I   E   L   F   D   Q   I   D   E   N   L   K   L   A   L   Q   Q   D   L   T  157
ATC GAG CTG TTT GAT CAA ATT GAT GAA AAC CTC AAG TTG GCT TTG CAG CAG GAC CTG ACT  637

 S   M   A   P   G   L   V   I   Q   A   V   R   V   T   K   P   N   I   P   E  177
TCC ATG GCC CCT GGG CTG GTT ATC CAA GCT GTG CGA GTG ACA AAG CCC AAT ATA CCT GAG  697

 A   I   R   R   N   Y   E   L   M   E   S   E   K   T   K   L   L   I   A   A  197
GCA ATC CGC AGG AAC TAT GAG CTG ATG GAA AGC GAG AAG ACG AAG CTT CTC ATT GCA GCC  757

 Q   K   Q   K   V   V   E   K   E   A   E   T   E   R   K   K   A   L   I   E  217
CAG AAG CAG AAG GTG GTG GAA AAG GAG GCA GAA ACA GAG AGG AAG AAG GCC CTC ATT GAG  817

 A   E   K   V   A   Q   V   A   E   I   T   Y   G   Q   K   V   M   E   K   E  237
GCA GAA AAA GTG GCA CAG GTT GCA GAA ATC ACC TAT GGG CAA AAG GTG ATG GAG AAG GAG  877

 T   E   K
ACA GAG AAG
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FIG. 6

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                                                                M   N   M   T   Q   A   R   V      8
GTCGACCCACGCGTCCGGCGGCTGGGCTTCTTCTCAGAGGAACGAGA ATG AAT ATG ACT CAA GCC CGG GTT     71

 L   V   A   A   V   V   G   L   V   A   V   L   L   Y   A   S   I   H   K   I     28
CTG GTG GCT GCA GTG GTG GGG TTG GTG GCT GTC CTG CTC TAC GCC TCC ATC CAC AAG ATT    131

 E   E   G   H   L   A   V   Y   Y   R   G   G   A   L   L   T   S   P   S   G     48
GAG GAG GGC CAT CTG GCT GTG TAC TAC AGG GGA GGA GCT TTA CTA ACT AGC CCC AGT GGA    191

 P   G   Y   H   I   M   L   P   F   I   T   T   F   R   S   V   Q   T   T   L     68
CCA GGC TAT CAT ATC ATG TTG CCT TTC ATT ACT ACG TTC AGA TCT GTG CAG ACA ACA CTA    251

 Q   T   D   E   V   K   N   V   P   C   G   T   S   G   G   V   M   I   Y   I     88
CAA ACT GAT GAA GTT AAA AAT GTG CCT TGT GGA ACA AGT GGT GGG GTC ATG ATC TAT ATT    311

 D   R   I   E   V   V   N   M   L   A   P   Y   A   V   F   D   I   V   R   N    108
GAC CGA ATA GAA GTG GTT AAT ATG TTG GCT CCT TAT GCA GTG TTT GAT ATC GTG AGG AAC    371

 Y   T   A   D   Y   D   K   T   L   I   F   N   K   I   H   H   E   L   N   Q    128
TAT ACT GCA GAT TAT GAC AAG ACC TTA ATC TTC AAT AAA ATC CAC CAT GAG CTG AAC CAG    431

 F   C   S   A   H   T   L   Q   E   V   Y   I   E   L   F   D   Q   I   D   E    148
TTC TGC AGT GCC CAC ACA CTT CAG GAA GTT TAC ATT GAA TTG TTT GAT CAA ATA GAT GAA    491

 N   L   K   Q   A   L   Q   K   D   L   N   L   M   A   P   G   L   T   I   Q    168
AAC CTG AAG CAA GCT CTG CAG AAA GAC TTA AAC CTC ATG GCC CCA GGT CTC ACT ATA CAG    551

 A   V   R   V   T   K   P   K   I   P   E   A   I   R   R   N   F   E   L   M    188
GCT GTG CGT GTT ACA AAA CCC AAA ATC CCA GAA GCC ATA AGA AGA AAT TTT GAG TTA ATG    611

 E   A   E   K   T   K   L   L   I   A   A   Q   K   Q   K   V   V   E   K   E    208
GAG GCT GAG AAG ACA AAA CTC CTT ATA GCT GCA CAG AAA CAA AAG GTT GTG GAA AAA GAA    671

 A   E   T   E   R   K   K   A   V   I   E   A   E   K   I   A   Q   V   A   K    228
GCT GAG ACA GAG AGG AAA AAG GCA GTT ATA GAA GCA GAG AAG ATT GCA CAA GTG GCA AAA    731

 I   R   F   Q   Q   K   V   M   E   K   E   T   E   K   R   I   S   E   I   E    248
ATT CGG TTT CAG CAG AAA GTG ATG GAA AAA GAA ACT GAA AAG CGC ATT TCT GAA ATC GAA    791

 D   A   A   F   L   A   R   E   K   A   K   A   D   A   E   Y   Y   A   A   H    268
GAT GCT GCA TTC CTG GCC CGA GAG AAA GCG AAA GCA GAT GCT GAA TAT TAT GCT GCA CAC    851

 K   Y   A   T   S   N   K   H   K   L   T   P   E   Y   L   E   L   K   K   Y    288
AAA TAT GCC ACC TCA AAC AAG CAC AAG TTG ACC CCG GAA TAT CTG GAG CTC AAA AAG TAC    911

 Q   A   I   A   S   N   S   K   I   Y   F   G   S   N   I   P   N   M   F   V    308
CAG GCC ATT GCT TCT AAC AGT AAG ATC TAT TTT GGC AGC AAC ATC CCT AAC ATG TTC GTG    971

 D   S   S   C   A   L   K   Y   S   D   I   R   T   G   R   E   S   S   L   P    328
GAC TCC TCA TGT GCT TTG AAA TAT TCA GAT ATT AGG ACT GGA AGA GAA AGC TCA CTC CCC   1031

 S   K   E   A   L   E   P   S   G   E   N   V   I   Q   N   K   E   S   T   G    348
TCT AAG GAG GCT CTT GAA CCC TCT GGA GAG AAC GTC ATC CAA AAC AAA GAG AGC ACA GGT   1091

 *                                                                                 349
TGA                                                                               1094
```

Fig. 5 1 of 2

TGCAAGAGGTGGAAATGTTCTCCATATCAAGATGTGGCCCAAGGGGTTAAGTGGGAACAATCATTATACGGACTCTTCA 1173

GATTTACAGAGAACTTACACTTCATCTGTTCCACCTCTCCTGCGATAGTCCTGGGTGCTCCACTGATTGGAGGATAGAG 1252

CCAGCTGTCTGACACACAAATGGTCTTTTCAGCCACAGTCTTATCAAGTATCCTATATGTATTCCTTTCTAAACTGCTA 1331

CTCATGAATGAGGAAAGTCTGATGCTAAGATACTGCCTGCATTCCCTGCATTGGGTTGATGACTGTCAGCATCACTGCC 1410

GCAGGCCATGCTTGACTAAGGTACCTGGTTTTAGCCACAGCCACCTCCTTGTATGTTACCTTTCAGCTCTGGCCAAGAG 1489

TGGGACAGGGTTTTAACCACAAATAGGAGCAGCATGCAATTCCTAGTGACTTGCTGCACAGTATTGTATCATAATTACA 1568

GGAAGTTTTTATTTTTAAAACTGGATCTGGGGTATATTCATTTGCCCCATCACCTCTGTCTAAAGGCCCAAGTCCTAGG 1647

GCTGCCATGGTCACAAGCACACTGATGCTCCTTAAGATTGTTTATCTGGAGCCCACATAGTGTGGAACAAAAAGTCACC 1726

TAGAAAGCATCCTTGGTCATCATTGTCTCCTTCCCACCTGGCCCAGAGATGCTTAAATCCAAGTTGTTTCTCCAGCTGT 1805

CACCTCCCCCAGGAGATCAGGATTCCACTGACGTCCTGGGCAGCCAGTGAATTTAATTTTCCATGAGAAACAACAGAGT 1884

TAACCTGTGGCATTAGGAGACCTACTTCATGTGGACCCTTTTTTTCCTTCAGTTTAACTTTTCTGGAGCAGTGTGCTGC 1963

GTAGTTCGGCCTGAGTTTGTGCAGCTTGTTAAGACAACTCTTGTGTACACTATGTTGAAGCTCAACAAAAAAGTCATGG 2042

GACCACTTCTAGAAATCTTTCAGCTGTCAGGCCTGTCAGTCTCATGACAGTTTGTTGGTTGTGCCAAACACTTTATTTG 2121

GGAAAGGAAAGCCCAGATTTGAATGGGTCTTTCCCCTGGGCCTTATCCTATAGAGGCATTTGTAATATGGAGAAAATAA 2200

TTTTTCATTTTTGCTCATTTAATTCTATAAATTCTCTTTATAAATGAATTTTGTGTTCTTTAGTTCTCCTTAAAAGAAC 2279

TTTTGAATTATAAAAATAAAATCTTTACCTGTCGAATTGTTGCTGCAGATGATTGTTGTGGAAAATCTGGATCATTGAC 2358

CTCTGTGCTTTCATTCCTAGAGATGTTTTATAGTTACATGAGCAAAAGCTGTTGCCCCAAAGTGATGGCCCTGGAGGCG 2437

GGGCTGAGGAACAGGGAAATGCCGCTGTGAAGTCTTAAAGCACTTCTGCTTAAACTCCATGTGTGAGGAGTGTGCCTCC 2516

CTGTGCCCTCTCAGCTCTGAGGCTGGCCGTCTTTCGGGGTGTTCCTTTTGGCAAATATACACTGTAATCTTGAGTCTAA 2595

ATTTATATGTTGAAATGCTACCTTTTTTAAAATAAGAAACTAAATAAAATTATTTTACTATCAAAAAAAAAAAAAAAAA 2674

AAAAAAAAAAAAAAAAAAAAAAAAAAAAAA 2704

FIG. 5 (SHEET)

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                                                          M  I  Y  I  D  R  I     7
GTCGACCCACGCGTCCGTAAAAATGTGCCTTGTGGAACAAGTGGTGGAGTC ATG ATC TAT ATT GAC CGA ATA   72

 E  V  V  N  M  L  A  P  Y  A  V  F  D  I  V  R  N  Y  T  A    27
GAA GTG GTT AAT ATG TTG GCT CCT TAT GCA GTG TTT GAC ATT GTG AGG AAC TAT ACT GCA  132

 D  Y  D  K  T  L  I  F  N  K  I  H  H  E  L  N  Q  F  C  S    47
GAC TAC GAC AAG ACT TTA ATC TTC AAT AAA ATC CAC CAT GAG CTG AAC CAG TTT TGC AGT  192

 A  H  T  L  Q  E  V  Y  I  E  L  F  D  Q  I  D  E  N  L  K    67
GCC CAC ACA CTT CAA GAA GTT TAC ATA GAA TTG TTT GAT CAA ATA GAT GAA AAC CTG AAG  252

 Q  A  L  Q  K  D  L  N  T  M  A  P  G  L  T  I  Q  A  V  R    87
CAG GCC CTG CAA AAA GAT TTA AAC ACC ATG GCC CCA GGT CTC ACT ATC CAG GCT GTG CGT  312

 V  T  K  P  K  I  P  E  A  I  R  R  N  F  E  L  M  E  A  E   107
GTT ACA AAA CCC AAA ATC CCA GAA GCC ATA AGA AGA AAT TTT GAA TTA ATG GAG GCA GAG  372

 K  T  K  L  L  I  A  A  Q  K  Q  K  V  V  E  K  E  A  E  T   127
AAG ACA AAA CTT CTC ATA GCT GCA CAG AAA CAA AAG GTG GTG GAG AAA GAA GCT GAG ACG  432

 E  R  K  R  A  V  I  E  A  E  K  I  A  Q  V  A  K  I  R  F   147
GAG AGG AAA AGG GCT GTT ATA GAA GCA GAG AAG ATT GCA CAA GTA GCA AAA ATT CGA TTT  492

 Q  Q  K  V  M  E  K  E  T  E  K  R  I  S  E  I  E  D  A  A   167
CAA CAG AAA GTG ATG GAG AAA GAA ACT GAA AAA CGC ATT TCT GAG ATT GAA GAT GCT GCG  552

 F  L  A  R  E  K  A  K  A  D  A  E  Y  Y  A  A  H  K  Y  A   187
TTC CTG GCC CGA GAG AAG GCA AAA GCA GAT GCC GAG TAT TAC GCT GCA CAC AAA TAC GCC  612

 T  S  N  K  H  K  L  T  P  E  Y  L  E  L  K  K  Y  Q  A  I   207
ACC TCA AAC AAG CAC AAA CTG ACC CCA GAG TAT CTG GAG CTC AAG AAA TAC CAG GCC ATT  672

 A  S  N  S  K  I  Y  F  G  S  N  I  P  S  M  F  V  D  S  S   227
GCC TCA AAC AGT AAG ATC TAC TTT GGC AGC AAC ATC CCC AGC ATG TTT GTG GAC TCC TCC  732

 C  A  L  K  Y  S  D  G  R  T  G  R  E  D  S  L  P  P  E  E   247
TGT GCT CTG AAA TAC TCT GAT GGT AGG ACT GGG AGA GAA GAC TCC CTT CCC CCA GAG GAG  792

 A  R  E  P  S  G  E  S  P  I  Q  N  K  E  N  A  G  *        265
GCC CGT GAG CCC TCT GGA GAG AGC CCC ATC CAA AAC AAG GAG AAC GCA GGT TGA          846

TGCAAGAGGTGGAAATGTTCTCCCATATCAAGATGCGACCCAAGGGGCTAAGTGGGAACAGTGGTTATGTGGACTCGTA  925

AGATTCACAGAGAATGTGTGCTCTGTTGTGATTCTCTTGTCATAGTCCTGGTTTGCCAGCTGACTACAGGATAGACCCA 1004

GCTGTCTGGCACTCAAACGGTCTCTGCAGCCACAGTTTTATCAAGTATCCTGTATGTGTTCCTTTGTAAACCGGTACTC 1083

ATGAATGAGGGAAAGTCTGATGCTAAGATACTGCCTGCACTGGAATGTCAAACACTATATAACAAGCTGTGGTTTTTAA 1162

AAGCTATTGAATAATGTTTACATTGGTCCCTGAGGACATGTGTGCTCAGACATTCAAGAGCTAGGAGGCCAGAGAGAAG 1241

ACCTTCAGAAAACGGTAAGTTAAAGAAGACAAGTGTCATCAGACACTTGGGACCCGGGCTCTCTTTAAAGTCTAGTCCC 1320

GGCATTCCTCCATGTGATTGACAGCCAGACCTCTGGGTTCCCAGGAAATTATCTTCCAGTTGAATGACCATTTACTTGA 1399
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FIG. 6 (1 of 2)

TACAAATTGTACCTTTCTGTTTTTCTAGTCAGGTTGGTGGCCTGCAGGGACGCGTACTTTGCCACCCGACCAGAGGTTC 1478

CTCGAAGATATTCCCAATCACTAGTTTATTGCGTTAGGAGACTCAGAGATATAGAAAGCAGCTGAAATTTAAGGGAGAT 1557

AAAGCCTGCACTGCACCAAAGCTACGGGTCCCTGTGTTTCCTCTATTCAGTGATGTCATCAACCTCACTGTCCCAGCCC 1636

ATGTGTGACTAAAGTGCCCCGGTTTTAGCCACAGACAACTGCTTAGATGTCACCTCTTGGCTGACCAAAGCTGGGACAGG 1715

GCTTTAACCAGACATAGGAGCAGTGTGCAATTCCTGATTCACTGCACAGTATTATGTCATAATTGCAGGAATTATTTTT 1794

TGTTTTTAAAACTGGATTTGGGGCACATTCATTCACCCCAACACTTCTATCTAAAGGCCAAGGTTCTAGGGCTGCTATG 1873

GTCACTAACACACTGATTCTCCTTAAAGTAATTCTCGAAGTGTGGAACAAAGTGACCGAGACAGCATCCTCAGTCATCT 1952

TTGTCTCCTTCCCTGGGATGCAGATACCGAAGTTGCTTTTCCAACTTTCGCCTCCGCTAGGAGATCAGAAAGAATTCTT 2031

GTGACTTCCTGGGCAGCCATTGAATTCATTTTCCATGAGAAGATGACAGAGTTAGCCTGTGGCTATAGGAGATCATGTC 2110

ATCCAGACCTTTTTGCCCATCACATTAACTTTCCTGGAATATTGTGCTGCACAGGTAGACCTGAATCTGCCCAGCTTGT 2189

TGACAGCTCTTGTGTATACTGTGTTGAAGCCAGACAGAAAAGTAATGGGGCCACTTCTGAAACCTCTCAGCTGTTGATC 2268

TCACAGCAGCTAAAGGGTTGTGCCAAACATTTTATTAAGAAAGTAAAGCCCAGATTTGAATGGGGGTTTTCCCTAGGCC 2347

TTATAGTATAGAGGCATTTGTAATATGGAGAAAATAATTTTTCTCATTT AATTATAGAAATTACCTTCAAACAGATTTT 2426

GTGTTCTTTGGCCCTTCAAATACTGGTGTTACATTGTTGCTGCAGATAAATGATGATTGTCGTGGGATATCTGGATCAC 2505

TGAGCTCTGTGCTTTCATTCCTAGAGATGTTTCTCATTCCCATTTAGTGAAATGCTGTTGCCCCAAAGTGATGGTTGTG 2584

GGATTTCTTACCGGTCATAGGCCCCGGTGAGGAGCAGGGAAGCGCCATTGTGAAAGATTAAAGAAAGCACTTCCACTTG 2663

AGCTCCTTATGGAGTGAGCTTCCCTGTGCCCACTCAGTGAACTAAGTCTGACCATCCTTCAGGGACGTTCCTTTTGGTA 2742

AATATACACTGTAATCTTTAAGTCTAAATTTATATGTGAAAGTTAACTTTTTTTAAAAACCTAAATAAAATTATTTTCC 2821

TATCAAAAAAAAAAAAAAAAAAAGGGCGGCCG 2851

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GTCGACCCACGCGTCCGGCGGGGACAACTGGGTCTTTTGCGGCTGCAGCGGGCTTGTAGGTGTCCGGCTTTGCTGGCCC   79

                      M   K   L   L   S   L   V   A   V   V   G   C   L   L   V     15
AGCAAGCCTGATAAGC ATG AAG CTC TTA TCT TTG GTG GCT GTG GTC GGG TGT TTG CTG GTG       140

 P   P   A   E   A   N   K   S   S   E   D   I   R   C   K   C   I   C   P   P    35
CCC CCA GCT GAA GCC AAC AAG AGT TCT GAA GAT ATC CGG TGC AAA TGC ATC TGT CCA CCT   200

 Y   R   N   I   S   G   H   I   Y   N   Q   N   V   S   Q   K   D   C   N   C    55
TAT AGA AAC ATC AGT GGG CAC ATT TAC AAC CAG AAT GTA TCC CAG AAG GAC TGC AAC TGC   260

 L   H   V   V   E   P   M   P   V   P   G   H   D   V   E   A   Y   C   L   L    75
CTG CAC GTG GTG GAG CCC ATG CCA GTG CCT GGC CAT GAC GTG GAG GCC TAC TGC CTG CTG   320

 C   E   C   R   Y   E   E   R   S   T   T   T   I   K   V   I   I   V   I   Y    95
TGC GAG TGC AGG TAC GAG GAG CGC AGC ACC ACC ACC ATC AAG GTC ATC ATT GTC ATC TAC   380

 L   S   V   V   G   A   L   L   L   Y   M   A   F   L   M   L   V   D   P   L   115
CTG TCC GTG GTG GGT GCC CTG TTG CTC TAC ATG GCC TTC CTG ATG CTG GTG GAC CCT CTG   440

 I   R   K   P   D   A   Y   T   E   Q   L   H   N   E   E   E   N   E   D   A   135
ATC CGA AAG CCG GAT GCA TAC ACT GAG CAA CTG CAC AAT GAG GAG GAG AAT GAG GAT GCT   500

 R   S   M   A   A   A   A   A   S   L   G   G   P   R   A   N   T   V   L   E   155
CGC TCT ATG GCA GCA GCT GCT GCA TCC CTC GGG GGA CCC CGA GCA AAC ACA GTC CTG GAG   560

 R   V   E   G   A   Q   Q   R   W   K   L   Q   V   Q   E   Q   R   K   T   V   175
CGT GTG GAA GGT GCC CAG CAG CGG TGG AAG CTG CAG GTG CAG GAG CAG CGG AAG ACA GTC   620

 F   D   R   H   K   M   L   S   *                                               184
TTC GAT CGG CAC AAG ATG CTC AGC TAG                                             647

ATGGGCTGGTGTGGTTGGGTCAAGGCCCCAACACCATGGCTGCCAGCTTCCAGGCTGGACAAAGCAGGGGGCTACTTCT  726

CCCTTCCCTCGGTTCCAGTCTTCCCTTTAAAAGCCTGTGGCATTTTTCCTCCTTCTCCCTAACTTTAGAAATGTTGTAC  805

TTGGCTATTTTGATTAGGGAAGAGGGATGTGGTCTCTGATCTCCGTTGTCTTCTTGGGTCTTTGGGGTTGAAGGGAGGG  884

GGAAGGCAGGCCAGAAGGGAATGGAGACATTCGAGGCGGCCTCAGGAGTGGATGCGATCTGTCTCTCCTGGCTCCACTC  963

TTGCCGCCTTCCAGCTCTGAGTCTTGGGAATGTTGTTACCCTTGGAAGATAAAGCTGGGTCTTCAGGAACTCAGTGTCT 1042

GGGAGGAAAGCATGGCCCAGCATTCAGCATGTGTTCCTTTCTGCAGTGGTTCTTTATCACCACCTCCCTCCCAGCCCCA 1121

GCGCCTCAGCCCCAGCCCCAGCTCCAGCCCTGAGGACAGCTCTGATGGGAGAGCTGGGCCCCCTGAGCCCACTGGGTCT 1200

TCAGGGTGCACTGGAAGCTGGTGTTCGCTGTCCCCTGTGCACTTCTCGCACTGGGGCATGGAGTGCCCATGCATACTCT 1279

GCTGCCGGTCCCCTCACCTGCACTTGAGGGGTCTGGGCAGTCCCTCCTCTCCCCAGTGTCCACAGTCACTGAGCCAGAC 1358

GGTCGGTTGGAACATGAGACTCGAGGCTGAGCGTGGATCTGAACACCACAGCCCCTGTACTTGGGTTGCCTCTTGTCCC 1437

TGAACTTCGTTGTACCAGTGCATGGAGAGAAAATTTTGTCCTCTTGTCTTAGAGTTGTGTGTAAATCAAGGAAGCCATC 1516

ATTAAATTGTTTTATTTCTCAAAAAAAAAAAAAAAAAAAAAGGGCGGCCG 1565
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Fig 7

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GTCGACCCACGCGTCCGGCCTGCTGATCAGTGGCGGCTGCGGCTGAGCTTGCAGGCATCTAGTCTTGCTGGCTCAGCAA   79

                M   K   L   L   C   L   V   A   V   V   G   C   L   L   V   P   P    17
GCCCGATAAGC ATG AAG CTG CTG TGT TTG GTG GCT GTG GTG GGG TGC TTG CTG GTG CCC CCA   141

 A   Q   A   N   K   S   S   E   D   I   R   C   K   C   I   C   P   P   Y   R    37
GCT CAA GCC AAC AAG AGC TCT GAA GAT ATC CGG TGC AAA TGC ATC TGT CCG CCT TAC AGA   201

 N   I   S   G   H   I   Y   N   Q   N   V   S   Q   K   D   C   N   C   L   H    57
AAC ATC AGC GGG CAC ATT TAC AAC CAG AAT GTG TCT CAG AAG GAC TGC AAC TGC CTG CAT   261

 V   V   E   P   M   P   V   P   G   H   D   V   E   A   Y   C   L   L   C   E    77
GTG GTG GAG CCC ATG CCA GTG CCT GGC CAC GAT GTG GAA GCC TAC TGC CTG CTC TGC GAG   321

 C   R   Y   E   E   R   S   T   T   T   I   K   V   I   I   V   I   Y   L   S    97
TGT AGG TAC GAG GAG CGT AGC ACC ACA ACC ATC AAG GTC ATT ATT GTC ATC TAC CTG TCT   381

 V   V   G   A   L   L   L   Y   M   A   F   L   M   L   V   D   P   L   I   R   117
GTG GTG GGG GCC CTC TTA CTC TAC ATG GCC TTC CTG ATG CTG GTG GAC CCG CTC ATC CGG   441

 K   P   D   A   Y   T   E   Q   L   H   N   E   E   E   N   E   D   A   R   T   137
AAG CCA GAT GCC TAT ACT GAG CAG CTG CAC AAT GAA GAG GAG AAT GAG GAT GCT CGC ACC   501

 M   A   T   A   A   A   S   I   G   G   P   R   A   N   T   V   L   E   R   V   157
ATG GCA ACA GCC GCT GCG TCC ATT GGA GGA CCC CGG GCA AAC ACT GTC CTG GAG CGG GTG   561

 E   G   A   Q   Q   R   W   K   L   Q   V   Q   E   Q   R   K   T   V   F   D   177
GAA GGC GCT CAG CAG CGG TGG AAG CTG CAG GTG CAG GAG CAG CGG AAG ACG GTC TTC GAC   621

 R   H   K   M   L   S   *                                                       184
CGA CAC AAG ATG CTC AGT TAG                                                     642

ATGGTTGCCATGATTGCATCAGAGACCTGGGCCATGGCTACCAGCTTCTGGGGCTCACTGCAGTCTTCCCTGGGTCTTC   721

CCTTCAAATGCCCATGGCGTTTATCCTTCTCCCTCTCTAGAAATGTACTCGACTGTTATAACGAGGGAGTGTGATTGGG   800

TCTCTGTAGGTCTCTGGGGGGTAGAGGGGAGGGGAGGGAAGGCAGAAGGGAACAGAGACATTTGAGGTGGCCACATGAT   879

TGGGTGGAATTCATCCCTCCTGTCTTCACCATTCCTCCCAGCTCCACATCTTAAGGATGCTTACGGGAGACGAAGCTGT   958

GTCATCAAGAGCTCAGTGGGTGCGAGGAAAGTATGATCCAGCGCTCAGCCTTCGCTCTAGGATGCTGTGGTCCCCATTC  1037

CCAGTTCCTTCAGTGCCAGTACTTTAACTTGGCCTACCCCAGTCTCAGGAACTGTTGTGGTGCCCCTGAGCCCACAGTC  1116

ATCTCCAGAGTCCACCTGGAAGCCTGTTCCCCTCTCCTCGGCTCCTGGTCCACCAGTGCATGGCAGTGCCCATGCATGC  1195

CGGCATATTCAGCAGCTGTCACCTTACTCCCATCCCAGGAGGCCGTAAGGCCTCCCACCTCTCCCCTGTGACTGCAGCT  1274

GCTGAGCCATAAAGTTGGACCATATGACACAAGGCCAATGGGGACCGGAGTACCATGGCTCCTGTCCTTGGATGGTCTC  1353

TTGTCCCTGAATTTCATTGTATCATGCATGGAGAGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  1432

AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGGGGGGC  1510
```

Fig. 8

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GAATTCGGCACGAGGGGATCCCCAGCCGGGTCCCAAGCCTGTGCCTGAGCCTGAGCCTGAGCCTGAGCCTGAGCCCGAG 79

                                                          M  A  T  L  W  G      6
CCGGGAGCCGGTCGCGGGGGCTCCGGGCTGTGGGACCGCTGGGCCCCCAGCG ATG GCG ACC CTG TGG GGA    149

 G  L  L  R  L  G  S  L  L  S  L  S  C  L  A  L  S  V  L  L    26
GGC CTT CTT CGG CTT GGC TCC TTG CTC AGC CTG TCG TGC CTG GCG CTT TCC GTG CTG CTG  209

 L  A  Q  L  S  D  A  A  K  N  F  E  D  V  R  C  K  C  I  C    46
CTG GCG CAG CTG TCA GAC GCC GCC AAG AAT TTC GAG GAT GTC AGA TGT AAA TGT ATC TGC  269

 P  P  Y  K  E  N  S  G  H  I  Y  N  K  N  I  S  Q  K  D  C    66
CCT CCC TAT AAA GAA AAT TCT GGG CAT ATT TAT AAT AAG AAC ATA TCT CAG AAA GAT TGT  329

 D  C  L  H  V  V  E  P  M  P  V  R  G  P  D  V  E  A  Y  C    86
GAT TGC CTT CAT GTC GTG GAG CCC ATG CCT GTG CGG GGG CCT GAT GTA GAA GCA TAC TGT  389

 L  R  C  E  C  K  Y  E  E  R  S  S  V  T  I  K  V  T  I  I   106
CTA CGC TGT GAA TGC AAA TAT GAA GAA AGA AGC TCT GTC ACA ATC AAG GTT ACC ATT ATA  449

 I  Y  L  S  I  L  G  L  L  L  L  Y  M  V  Y  L  T  L  V  E   126
ATT TAT CTC TCC ATT TTG GGC CTT CTA CTT CTG TAC ATG GTA TAT CTT ACT CTG GTT GAG  509

 P  I  L  K  R  R  L  F  G  H  A  Q  L  I  Q  S  D  D  D  I   146
CCC ATA CTG AAG AGG CGC CTC TTT GGA CAT GCA CAG TTG ATA CAG AGT GAT GAT GAT ATT  569

 G  D  H  Q  P  F  A  N  A  H  D  V  L  A  R  S  R  S  R  A   166
GGG GAT CAC CAG CCT TTT GCA AAT GCA CAC GAT GTG CTA GCC CGC TCC CGC AGT CGA GCC  629

 N  V  L  N  K  V  E  Y  A  Q  Q  R  W  K  L  Q  V  Q  E  Q   186
AAC GTG CTG AAC AAG GTA GAA TAT GCA CAG CAG CGC TGG AAG CTT CAA GTC CAA GAG CAG  689

 R  K  S  V  F  D  R  H  V  V  L  S  *                       199
CGA AAG TCT GTC TTT GAC CGG CAT GTT GTC CTC AGC TAA                            728

TTGGGAATTGAATTCAAGGTGACTAGAAAGAAACAGGCAGACAACTGGAAAGAACTGACTGGGTTTTGCTGGGTTTCAT  807

TTTAATACCTTGTTGATTTCACCAACTGTTGCTGGAAGATTCAAAACTGGAAGCAAAAACTTGCTTGATTTTTTTTTCT  886

TGTTAACGTAATAATAGAGACATTTTTAAAAGCACACAGCTCAAAGTCAGCCAATAAGTCTTTTCCTATTTGTGACTTT  965

TACTAATAAAAATAAATCTGCCTGTAAATTATCTTGAAGTCCTTTACCTGGAACAAGCACTCTCTTTTTCACCACATAG 1044

TTTTAACTTGACTTTCAAGATAATTTTCAGGGTTTTTGTTGTTGTTGTTTTTTGTTTGTTTGTTTTGGTGGGAGAGGGG 1123

AGGGATGCCTGGGAAGTGGTTAACAACTTTTTTCAAGTCACTTTACTAAACAAACTTTTGTAAATAGACCTTACCTTCT 1202

ATTTTCGAGTTTCATTTATATTTTGCAGTGTAGCCAGCCTCATCAAAGAGCTGACTTACTCATTTGACTTTTGCACTGA 1281

CTGTGTTATCTGGGTATCTGCTGTGTCTGCACTTCATGGTAAACGGGATCTAAAATGCCTGGTGGCTTTTCACAAAAAG 1360

CAGATTTTCTTCATGTACTGTGATGTCTGATGCAATGCATCCTAGAACAAACTGGCCATTTGCTAGTTTACTCTAAAGA 1439

CTAAACATAGTCTTGGTGTGTGTGGTCTTACTCATCTTCTAGTACCTTTAAGGACAAATCCTAAGGACTTGGACACTTG 1518

CAATAAAGAAATTTTATTTTAAAAAAAAAAAAAAAAAAAAAAACTGCGGCCGC                          1569
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Fig. 1

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                                                                  M   A   S   L   W      5
GTCGACCCACGCGTCCGGGCGCGGGGCTCGGGGCTCGCAGGAGCGGCTGGCTCCCGCG ATG GCG AGC CTA TGG     73

 C   G   N   L   L   R   L   G   S   G   L   S   M   S   C   L   A   L   S   V     25
TGC GGA AAC CTG CTG CGG CTG GGC TCG GGG CTC AGC ATG TCC TGC CTG GCG CTG TCG GTG    133

 L   L   L   A   Q   L   T   G   A   A   K   N   F   E   D   V   R   C   K   C     45
CTG CTG CTC GCG CAG CTG ACA GGC GCC GCC AAG AAT TTT GAA GAT GTG AGA TGT AAA TGC    193

 I   C   P   P   Y   K   E   N   P   G   H   I   Y   N   K   N   I   S   Q   K     65
ATC TGC CCT CCC TAT AAA GAG AAT CCT GGG CAC ATT TAT AAT AAG AAT ATA TCT CAG AAA    253

 D   C   D   C   L   H   V   V   E   P   M   P   V   R   G   P   D   V   E   A     85
GAT TGT GAT TGC CTT CAT GTC GTG GAG CCC ATG CCT GTA CGG GGA CCT GAT GTA GAA GCA    313

 Y   C   L   R   C   E   C   K   Y   E   E   R   S   S   V   T   I   K   V   T    105
TAC TGT CTA CGC TGT GAA TGC AAA TAC GAA GAG AGA AGC TCT GTC ACA ATC AAG GTT ACC    373

 I   I   I   Y   L   S   I   L   G   L   L   L   L   Y   M   V   Y   L   T   L    125
ATT ATA ATT TAT CTC TCT ATT TTG GGC CTT CTG CTT CTG TAC ATG GTA TAT CTT ACC TTA    433

 V   E   P   I   L   K   R   R   L   F   G   H   S   Q   L   L   Q   S   D   D    145
GTT GAG CCC ATC CTG AAG AGG CGC CTC TTT GGA CAC TCC CAG CTG TTG CAG AGC GAT GAT    493

 D   V   G   D   H   Q   P   F   A   N   A   H   D   V   L   A   R   S   R   S    165
GAC GTT GGG GAT CAC CAG CCT TTT GCA AAT GCC CAT GAT GTG CTG GCC CGC TCT CGC AGC    553

 R   A   N   V   L   N   K   V   E   Y   A   Q   Q   R   W   K   L   Q   V   Q    185
CGA GCC AAT GTT CTA AAC AAG GTG GAG TAC GCT CAG CAG CGC TGG AAG CTC CAG GTC CAG    613

 E   Q   R   K   S   V   F   D   R   H   V   V   L   S   *                        200
GAG CAG CGA AAG TCT GTC TTC GAC CGA CAC GTT GTC CTC AGC TAA                        658

CTGGGAACTGGAATCAGGTGACTAGGAAGAACACGCAGACAACTGGGAAGAATTGTCTGGGTGTCCGTGCGTTTTAATG  737

CCATGTTTGTTTTTACAAATCCTTGCTGGATGGAGGAAGACTCCAAACTGGAAGCAAACCCCATGCTTGGTATTTTCCT  816

GTTAATATATTAATAGAGACATTTTTACAGCACACAGTTCCAAGTCAACCAGTAAGTCTTTTCCTACTTGTGACTTTTA  895

CTAATAAAATTAAGCTGCCTGTGAGTTATCTTGAAGCCCCGTGCCTGGAACAAGCTCTCTCTTTCTTGCCACACAGTTC  974

TAACTTGGTGTTCAAGATAACTTCCAGGTGTGTTTTTGCTTCTCTTTCTTGTGGTGGGAGAGAGAAGGAAGGATGCCTT 1053

GGGAGTGCTTGAGTAGCTTCTCAAGTGTCTTTTCCAGACAGACTTATGAATACTTCAGACCCTCTACTTCACACTTGTT 1132

AATGTCCCAGTGTAGCTGGCTTGTCAGCGTGCTGGCCTCCCCACTTGACTTTTGCACTGACTACATTACCTAAGATTCT 1211

GGTTAGCCTGTGGCTGCATTTCATGACCAGTTGGATCTGAAATGCCTGGGGGCTCCTCACAAAATGAAGATTTGTTTCA 1290

TGCACTGTGATGTCTGACGCAACATGTTCTAGAACAGACTGGCCATCTGCTAGTTTACACTGATACCTAAACACAGTCT 1369

CAGTGTGTGTGGTCTTCCTCATCTTCTTCTAGTAGCTCTAAGGACTTGAACATTTAGAATAAAGACATTTTCTCTTAAG 1448

CCCAAGCCTCCCTGGATGATTGACGTACAAATACTGATCAGCCTTTTCTGTCTTGCTGAGAGGCAGTTCTTTGAACTGA 1527

TGTGGGCAGCTTTGAACAAGGACTAGAGTTCAGATTGCCTCTCTCTGAGAAGTCTAACAGTTATTGGATAACTGGCTTT 1606
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FIG 10 (1 of 2)

TTTCTTCCTACATCCTCTTTGGAATGTAACAATAAAATAATTTACAAAACCCAAAAAAAAAAAAAAAGGGCGGCCG 1681

FIG 10 (2 of 2)

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GTCGACCCACGCGTCCGCTCTGAGTCACCGGAATCTAGGTGGGGCCGCCCGGAGCGGCGTCCTCGGGAGCCGCCTCCCC 79

GCGGCCTCTTCGCTTTTGTGGCGGCGCCCGCGCTCGCAGGCCACTCTCTGCTGTCGCCCGTCCCGCGCGCTCCTCCGAC 158

                                                M  I  R  C  G  L  A  C  E      9
CCGCTCCGCTCCGCTCCGCTCGGCCCCGCGCCGCCCGTCAAC ATG ATC CGC TGC GGC CTG GCC TGC GAG   227

 R  C  R  W  I  L  P  L  L  L  L  S  A  I  A  F  D  I  I  A     29
CGC TGC CGC TGG ATC CTG CCC CTG CTC CTA CTC AGC GCC ATC GCC TTC GAC ATC ATC GCG  287

 L  A  G  R  G  W  L  Q  S  S  D  H  G  Q  T  S  S  L  W  W     49
CTG GCC GGC CGC GGC TGG TTG CAG TCT AGC GAC CAC GGC CAG ACG TCC TCG CTG TGG TGG  347

 K  C  S  Q  E  G  G  G  S  G  S  Y  E  E  G  C  Q  S  L  M     69
AAA TGC TCC CAA GAG GGC GGC GGC AGC GGG TCC TAC GAG GAG GGC TGT CAG AGC CTC ATG  407

 E  Y  A  W  G  R  A  A  A  A  M  L  F  C  G  F  I  I  L  V     89
GAG TAC GCG TGG GGT AGA GCA GCG GCT GCC ATG CTC TTC TGT GGC TTC ATC ATC CTG GTG  467

 I  C  F  I  L  S  F  F  A  L  C  G  P  Q  M  L  V  F  L  R    109
ATC TGT TTC ATC CTC TCC TTC TTC GCC CTC TGT GGA CCC CAG ATG CTT GTC TTC CTG AGA  527

 V  I  G  G  L  L  A  L  A  A  V  F  Q  I  I  S  L  V  I  Y    129
GTG ATT GGA GGT CTC CTT GCC TTG GCT GCT GTG TTC CAG ATC ATC TCC CTG GTA ATT TAC  587

 P  V  K  Y  T  Q  T  F  T  L  H  A  N  P  A  V  T  Y  I  Y    149
CCC GTG AAG TAC ACC CAG ACC TTC ACC CTT CAT GCC AAC CCT GCT GTC ACT TAC ATC TAT  647

 N  W  A  Y  G  F  G  W  A  A  T  I  I  L  I  G  C  A  F  F    169
AAC TGG GCC TAC GGC TTT GGG TGG GCA GCC ACG ATT ATC CTG ATT GGC TGT GCC TTC TTC  707

 F  C  C  L  P  N  Y  E  D  D  L  L  G  N  A  K  P  R  Y  F    189
TTC TGC TGC CTC CCC AAC TAC GAA GAT GAC CTT CTG GGC AAT GCC AAG CCC AGG TAC TTC  767

 Y  T  S  A  *                                                   194
TAC ACA TCT GCC TAA                                              782

CTTGGGAATGAATGTGGGAGAAAATCGCTGCTGCTGAGATGGACTCCAGAAGAAGAAACTGTTTCTCCAGGCGACTTTG  861

AACCCATTTTTTGGCAGTGTTCATATTATTAAACTAGTCAAAAATGCTAAAATAATTTGGGAGAAAATATTTTTTAAGT  940

AGTGTTATAGTTTCATGTTTATCTTTTATTATGTTTTGTGAAGTTGTGTCTTTTCACTAATTACCTATACTATGCCAAT 1019

ATTTCCTTATATCTATCCATAACATTTATACTACATTTGTAAGAGAATATGCACGTGAAACTTAACACTTTATAAGGTA 1098

AAAATGAGGTTTCCAAGATTTAATAATCTGATCAAGTTCTTGTTATTTCCAAATAGAATGGACTCGGTCTGTTAAGGGC 1177

TAAGGAGAAGAGGAAGATAAGGTTAAAAGTTGTTAATGACCAAACATTCTAAAAGAAATGCAAAAAAAAAAGTTTATTTT 1256

CAAGCCTTCGAACTATTTAAGGAAAGCAAAATCATTTCCTAAATGCATATCATTTGTGAGAATTTCTCATTAATATCCT 1335

GAATCATTCATTTTAGCTAAGGCTTCATGTTGACTCGATATGTCATCTAGGAAAGTACTATTTCATGGTTCAAACCTGT 1414

TGCCATAGTTGGTAAGGCTTTCCTTTAAGTGTGAAATATTTAGATGAAATTTTCTCTTTTAAAGTTCTTTATAGGGTTA 1493

GGGTGTGGGAAAATGCTATATTAATAAATCTGTAGTGTTTTGTGTTTATATGTTCAGAACCAGAGTAGACTGGATTGAA 1572

AGATGGACTGGGTCTAATTTATCATGACTGATAGATCTGGTTAAGTTGTGTAGTAAAGCATTAGGAGGGTCATTCTTGT 1651
```

Fig. 11 (1 of 2)

CACAAAAGTGCCACTAAAACAGCCTCAGGAGAATAAATGACTTGCTTTTCTAAATCTCAGGTTTATCTGGGCTCTATCA 1730

TATAGACAGGCTTCTGATAGTTTGCAACTGTAAGCAGAAACCTACATATAGTTAAAATCCTGGTCTTTCTTGGTAAACA 1809

GATTTTAAATGTCTGATATAAAACATGCCACAGGAGAATTCGGGGATTTGAGTTTCTCTGAATAGCATATATATGATGC 1888

ATCGGATAGGTCATTATGATTTTTTACCATTTCGACTTACATAATGAAAACCAATTCATTTTAAATATCACGATTATTA 1967

TTTTGTAAGTTGTGGAAAAAGCTAATTGTAGTTTTCATTATGAAGTTTTCCCAATAAACCAGGGCATTCTAAAAAAAAA 2046

AAAAAAAAAAAGGGCGGCCGC
2067

FIG. 11 (2 OF 2)

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GTCGACCCACGCGTCCGGCGCTCTGAGTCACCGGAATCAAGGTGTGGCTGGAGCGCCGCTCCCCCGCCGCCAGCCCGGG  79

GGCCGCGTCTTCGGGGGAGCCGCCTCTTCCTTTAGTCGCGGTGTCAGCGCTCGCAGGACCACTCTTGGCCGCTGCTCCT 158

                                                  M  L  R  C  G  L  A  C  E       9
GCCCGGCGTTCCTCCGCTCCGCGCCCGCCGCCACCGACGAC ATG CTG CGC TGC GGC CTG GCC TGC GAG     226

 R  C  R  W  I  L  P  L  L  L  L  S  A  I  A  F  D  I  I  A     29
CGC TGC AGG TGG ATC CTG CCC CTG CTG CTG CTC AGC GCC ATC GCC TTC GAC ATC ATC GCG  286

 L  A  G  R  G  W  L  Q  S  S  N  H  I  Q  T  S  S  L  W  W     49
CTG GCC GGC CGC GGC TGG CTG CAG TCT AGC AAC CAC ATC CAG ACA TCG TCG CTT TGG TGG  346

 R  C  F  D  E  G  G  G  S  G  S  Y  D  D  G  C  Q  S  L  M     69
AGG TGT TTC GAC GAG GGC GGC GGC AGC GGC TCC TAC GAC GAT GGC TGC CAG AGC CTC ATG  406

 E  Y  A  W  G  R  A  A  A  A  T  L  F  C  G  F  I  I  L  C     89
GAG TAC GCA TGG GGA CGA GCA GCT GCA GCC ACG CTT TTC TGT GGC TTT ATC ATC CTG TGC  466

 I  C  F  I  L  S  F  F  A  L  C  G  P  Q  M  L  V  F  L  R    109
ATC TGC TTC ATT CTC TCG TTC TTC GCC CTG TGT GGA CCC CAG ATG CTT GTT TTC CTG AGA  526

 V  I  G  G  L  L  A  L  A  A  I  F  Q  I  I  S  L  V  I  Y    129
GTC ATT GGA GGC CTC CTC GCA CTG GCT GCC ATA TTC CAG ATC ATC TCC CTG GTA ATC TAC  586

 P  V  K  Y  T  Q  T  F  R  L  H  D  N  P  A  V  N  Y  I  Y    149
CCC GTG AAG TAC ACA CAG ACC TTC AGG CTT CAC GAT AAC CCT GCT GTT AAT TAC ATC TAT  646

 N  W  A  Y  G  F  G  W  A  A  T  I  I  L  I  G  C  S  F  F    169
AAC TGG GCC TAT GGC TTC GGA TGG GCG GCC ACC ATC ATC TTG ATT GGT TGT TCC TTC TTC  706

 F  C  C  L  P  N  Y  E  D  D  L  L  G  A  A  K  P  R  Y  F    189
TTC TGC TGC CTC CCC AAC TAC GAG GAT GAC CTT TTG GGG GCC GCC AAG CCC AGG TAC TTC  766

 Y  P  P  A  *                                                   194
TAT CCC CCA GCC TAA                                              781

TGTGGGAGGAAGAGCCTGAGAAAAGCCTGCTGCAAGATGGATCTGAGGAGGAAACTGTTCTCCAAGGCACAAGGAACCT  860

ACGTTTGGGCAATGTTCATATGATCAGAAATGCTAGAATAAATGCTAAAGAAAATTCTTCATAATTAGTGTTAAGTTTC  939

ATGTATGTCGTGTGGAGTTAAAAAAGACTTGAATTCTGTTTGCTAAGTATATGCTAATTTTTCCTTATGTCAATTCTATA 1018

CCATTTAAGCTTCATTTGTTAAAGAATATGCCTGTGAAACTTGATAAGGTAGAAATGTAGCAGCCTCTCATTTAATAAT 1097

CTGATGGGGCTTCTGTTTTTCCACATAGAATGGGTTGTTTCTGCTAAGGGCTACAGAGGAGGAAAGTCACTGGCAAAAC 1176

TTCCGTGACCAAATATCCTGAAATTAGTATTTTTTTAAAAAGACCTTATTTTGAGTTTTCAGTTACATAAAAAAGCAGA 1255

AGCAGATTGGTTTCCTAAGTGAGCATCGTTTGTGAGAATTTTTAGTCAGTGTTTTGAACAATTATTGTTTTTCTAAGCT 1334

TCGTGTTGACTTTCTCTGATGCGTAGAAAAGTGTTCTAACGTAGCCAAGGTTAAGCCGCTGTCACTACTGAAATGCTAA 1413

GAATTTTCCTCTTTTCCCGTAGTGTAGAGGGGTAGGGTGTGGGAAGAAGCCGTGTTAGCACATCTGTAGTATTCTGTGT 1492

GTATGCTTAGAACCAGCGTAGACCGGATGGGAGGATGGACTAGGCCTAATCCCTCCCAACTGGTGGATGTGAAGAGGTC 1571
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FIG. 12 (1 of 2)

AGGTAGGAAGGCACAGGAGGGTCACCACTGTCACAGCAGTGCCATGCAGACATCCTAGGAGAAGACATGGCAGTGTTTC 1650

TTCTCAGTGCTTCTTCCCTTAACTGAGCTCTGCTCACAGACAGCTAGAATAGATTTTAACTGTAACAGAAACCTAAATG 1729

TAATTAAAACCTGGTCTTCCTTGGTAAGCAGACTTAAAATATCTGTATAGTACATGCAAGTGGAAAATTTGGGAATGCG 1808

TGTCTCTGAATACATACCGGAAGGGCTACTATTACCTTTTCCTTACCATTTATACTTACCTAATGGAAACGAGCTTGTT 1887

TTAACTATCAGAACACTATTTTGTAAGGTGCTGCAAAGACAGTTGAAGTTTTCATTACCAACTTCCCCAATAAACCAGG 1966

TGTTCAAAAAAAAAAAAAAAAACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGGGCGGCCGC 2030

FIG 12 (2 OF 2)

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GTCGACCCACGCGTCCGGCCGCGCGCTCTCTCCCGGCGCCCACACCTGTCTGAGCGGCGCAGCGAGCCGCGGCCCGGGC      79

                                    M   A   G   I   P   G   L   L   F   L   L   F      12
GGGCTGCTCGGCGCGGAACAGTGCTCGGC ATG GCA GGG ATT CCA GGG CTC CTC TTC CTT CTC TTC      144

  F   L   L   C   A   V   G   Q   V   S   P   Y   S   A   P   W   K   P   T   W      32
TTT CTG CTC TGT GCT GTT GGG CAA GTG AGC CCT TAC AGT GCC CCC TGG AAA CCC ACT TGG      204

  P   A   Y   R   L   P   V   V   L   P   Q   S   T   L   N   L   A   K   P   D      52
CCT GCA TAC CGC CTC CCT GTC GTC TTG CCC CAG TCT ACC CTC AAT TTA GCC AAG CCA GAC      264

  F   G   A   E   A   K   L   E   V   S   S   S   C   G   P   Q   C   H   K   G      72
TTT GGA GCC GAA GCC AAA TTA GAA GTA TCT TCT TCA TGT GGA CCC CAG TGT CAT AAG GGA      324

  T   P   L   P   T   Y   E   E   A   K   Q   Y   L   S   Y   E   T   L   Y   A      92
ACT CCA CTG CCC ACT TAC GAA GAG GCC AAG CAA TAT CTG TCT TAT GAA ACG CTC TAT GCC      384

  N   G   S   R   T   E   T   Q   V   G   I   Y   I   L   S   S   S   G   D   G     112
AAT GGC AGC CGC ACA GAG ACG CAG GTG GGC ATC TAC ATC CTC AGC AGT AGT GGA GAT GGG      444

  A   Q   H   R   D   S   G   S   S   G   K   S   R   R   K   R   Q   I   Y   G     132
GCC CAA CAC CGA GAC TCA GGG TCT TCA GGA AAG TCT CGA AGG AAG CGG CAG ATT TAT GGC      504

  Y   D   S   R   F   S   I   F   G   K   D   F   L   L   N   Y   P   F   S   T     152
TAT GAC AGC AGG TTC AGC ATT TTT GGG AAG GAC TTC CTG CTC AAC TAC CCT TTC TCA ACA      564

  S   V   K   L   S   T   G   C   T   G   T   L   V   A   E   K   H   V   L   T     172
TCA GTG AAG TTA TCC ACG GGC TGC ACC GGC ACC CTG GTG GCA GAG AAG CAT GTC CTC ACA      624

  A   A   H   C   I   H   D   G   K   T   Y   V   K   G   T   Q   K   L   R   V     192
GCT GCC CAC TGC ATA CAC GAT GGA AAA ACC TAT GTG AAA GGA ACC CAG AAG CTT CGA GTG      684

  G   F   L   K   P   K   F   K   D   G   G   R   G   A   N   D   S   T   S   A     212
GGC TTC CTA AAG CCC AAG TTT AAA GAT GGT GGT CGA GGG GCC AAC GAC TCC ACT TCA GCC      744

  M   P   E   Q   M   K   F   Q   W   I   R   V   K   R   T   H   V   P   K   G     232
ATG CCC GAG CAG ATG AAA TTT CAG TGG ATC CGG GTG AAA CGC ACC CAT GTG CCC AAG GGT      804

  W   I   K   G   N   A   N   D   I   G   M   D   Y   D   Y   A   L   L   E   L     252
TGG ATC AAG GGC AAT GCC AAT GAC ATC GGC ATG GAT TAT GAT TAT GCC CTC CTG GAA CTC      864

  K   K   P   H   K   R   K   F   M   K   I   G   V   S   P   P   A   K   Q   L     272
AAA AAG CCC CAC AAG AGA AAA TTT ATG AAG ATT GGG GTG AGC CCT CCT GCT AAG CAG CTG      924

  P   G   G   R   I   H   F   S   G   Y   D   N   D   R   P   G   N   L   V   Y     292
CCA GGG GGC AGA ATT CAC TTC TCT GGT TAT GAC AAT GAC CGA CCA GGC AAT TTG GTG TAT      984

  R   F   C   D   V   K   D   E   T   Y   D   L   L   Y   Q   Q   C   D   A   Q     312
CGC TTC TGT GAC GTC AAA GAC GAG ACC TAT GAC TTG CTC TAC CAG CAA TGC GAT GCC CAG     1044

  P   G   A   S   G   S   G   V   Y   V   R   M   W   K   R   Q   Q   Q   K   W     332
CCA GGG GCC AGC GGG TCT GGG GTC TAT GTG AGG ATG TGG AAG AGA CAG CAG CAG AAG TGG     1104

  E   R   K   I   I   G   I   F   S   G   H   Q   W   V   D   M   N   G   S   P     352
GAG CGA AAA ATT ATT GGC ATT TTT TCA GGG CAC CAG TGG GTG GAC ATG AAT GGT TCC CCA     1164
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FIG. 13 (1 OF 3)

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 Q  D  F  N  V  A  V  R  I  T  P  L  K  Y  A  Q  I  C  Y  W    372
CAG GAT TTC AAC GTG GCT GTC AGA ATC ACT CCT CTC AAA TAT GCC CAG ATT TGC TAT TGG   1224

 I  K  G  N  Y  L  D  C  R  E  G  *                              384
ATT AAA GGA AAC TAC CTG GAT TGT AGG GAG GGG TGA                   1260

CACAGTGTTCCCTCCTGGCAGCAATTAAGGGTCTTCATGTTCTTATTTTAGGAGAGGCCAAATTGTTTTTTGTCATTGG  1339

CGTGCACACGTGTGTGTGTGTGTGTGTGTGTAAGGTGTCTTATAATCTTTTACCTATTTCTTACAATTGCAAGATGACT  1418

GGCTTTACTATTTGAAAACTGGTTTGTGTATCATATCATATATCATTTAAGCAGTTTGAAGGCATACTTTTGCATAGAA  1497

ATAAAAAAAAATACTGATTTGGGGCAATGAGGAATATTTGACAATTAAGTTAATCTTCACGTTTTTGCAAACTTTGATTT  1576

TTATTTCATCTGAACTTGTTTCAAAGATTTATATTAAATATTTGGCATACAAGAGATATGAATTCTTATATGTGTGCAT  1655

GTGTGTTTTCTTCTGAGATTCATCTTGGTGGTGGGTTTTTTTGTTTTTTTAATTCAGTGCCTGATCTTTAATGCTTCCA  1734

TAAGGCAGTGTTCCCATTTAGGAACTTTGACAGCATTTGTTAGGCAGAATATTTTGGATTTGGAGGCATTTGCATGGTA  1813

GTCTTTGAACAGTAAAATGATGTGTTGACTATACTGATACACATATTAAACTATACCTTATAGTAAACCAGTATCCCAA  1892

GCTGCTTTTAGTTCCAAAAATAGTTTCTTTTCCAAAGGTTGTTGCTCTACTTTGTAGGAAGTCTTTGCATATGGCCCTC  1971

CCAACTTTAAAGTCATACCAGAGTGGCCAAGAGTGTTTATCCCAACCCTTCCATTTAACAGGATTTCACTCACATTTCT  2050

GGAACTAGCTATTTTTCAGAAGACAATAATCAGGGCTTAATTAGAACAGGCTGTATTTCCTCCCAGCAAACAGTTGTGG  2129

CCACACTAAAAACAATCATAGCATTTTACCCCTGGATTATAGCACATCTCATGTTTTATCATTTGGATGGAGTAATTTA  2208

AAATGAATTAAATTCCAGAGAACAATGGAAGCATTGCCTGGCAGATGTCACAACAGAATAACCACTTGTTTGGAGCCTG  2287

GCACAGTCCTCCAGCCTGATCAAAAATTATTCTGCATAGTTTTCAGTGTGCTTTCTGGGAGCTATGTACTTCTTCAATT  2366

TGGAAACTTTTCTCTCTCATTTATAGTGAAAATACTTGGAAGTTACTTTAAGAAAACCAGTGTGGCCTTTTTCCCTCTA  2445

GCTTTAAAAGGGCCGCTTTTGCTGGAATGCTCTAGGTTATAGATAAACAATTAGGTATAATAGCAAAAATGAAAATTGG  2524

AAGAATGCAAAATGGATCAGAATCATGCCTTCCAATAAAGGCCTTTACACATGTTTTATCAATATGATTATCAAATCAC  2603

AGCATATACAGAAAAGACTTGGACTTATTGTATGTTTTTATTTTATGGCTCTCGGCCTAAGCACTTCTTTCTAAATGTA  2682

TCGGAGAAAAAATCAAATGGACTACAAGCACGTGTTTGCTGTGCTTGCACCCCAGGTAAACCTGCATTGTAGCAATTTG  2761

TAAGGATATTCAGATGGAGCACTGTCACTTAGACATTCTCTGGGGGGATTTTCTGCTTGTCTTTCTTGAGCTTTTTGGAA  2840

GGATAATTCTGATAAGGCACTCAAGAAACGTACAACCACAGTGCTTTCTTCAAATCATATGAGAAATACTATGCATAGC  2919

AAGGAGATGCAGAGCCGCCAGGAAAATTCTGAGTTCCAGCACAATTTTCTTTGGAATCTAACAGGAATCTAGCCTGAGG  2998

AAGAAGGGAGGTCTCCATTTCTATGTCTGGTATTTGGGGGTTTTGTTTGTTTTTGCTTTAGCTTGGTGAAAAAAAGTTC  3077

ACTGAACACCAAGACCAGAATGGATTTTTTTAAAAAAATAGATGTTCCTTTTGTGAAGCACCTTGATTCCTTGATTTTG  3156

ATTTTTTGCAAAGTTAGACAATGGCACAAAGTCAAAATGAAATCAATGTTTAGTTCACAAGTAGATGTAATTTACTAAA  3235

GAATGATACACCCATATGCTATATACAGCTTAACTCACAGAACTGTAAAAGAAAATTATAAAATAATTCAACATGTCCA  3314

TCTTTTTAGTGATAATAAAAGAAAGCATGGTATTAAACTATCATAGAAGTAGACAGAAAAAGAAAAAAGGACTCATGGC  3393
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FIG 13 (2 of 3)

ATTATTAATATAATTAGTGCTTTACATGTGTTAGTTATACATATTAGAAGCATATTTGCCTAGTAAGGCTAGTAGAACC 3472

ACATTTCCCAAAGTGTGCTCCTTAAACACTCATGCCTTATGATTTTCTACCAAAAGTAAAAAGGGTTGTATTAAGTCAG 3551

AGGAAGATGCCTCTCCATTTTCCCTCTCTTTATCAGAGGTTCACATGCCTGTCTGCACATTAAAAGCTCTGGGAAGACC 3630

TGTTGTAAAGGGACAAGTTGAGGTTGTAAAATCTGCATTTAAATAAACATCTTTGATCACAAAAAAAAAAAAAAAGGGC 3709

GGCCG 3714

FIG 13 (3 OF 3)

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GTCGACCCACGCGTCCGCGGACGCGTGGGCACTCGGCCACTCTGCGGAGCAGGCATGGGAGCCGCGCGCGTCCTCCGGG      79

                                                                          M  A          2
CGCCCACACCTGTCTGAGCGGCGCACGGCCGCGGCCCCGGCGGGCTGCTCCACGCGGTAGCACTCAGC ATG GCT       153

 G  I  P  G  L  F  I  L  L  V  L  L  C  V  F  M  Q  V  S  P                       22
GGA ATC CCG GGG CTC TTC ATC CTT CTT GTC CTG CTC TGT GTG TTC ATG CAG GTG AGT CCC     213

 Y  T  V  P  W  K  P  T  W  P  A  Y  R  L  P  V  V  L  P  Q                       42
TAC ACC GTT CCG TGG AAA CCC ACA TGG CCG GCT TAT CGC CTC CCT GTA GTC TTG CCT CAG     273

 S  T  L  N  L  A  K  A  D  F  D  A  K  A  K  L  E  V  S  S                       62
TCT ACC CTC AAC TTA GCT AAG GCA GAC TTC GAC GCC AAA GCG AAA TTG GAG GTG TCC TCC     333

 S  C  G  P  Q  C  H  K  G  T  P  L  P  T  Y  E  E  A  K  Q                       82
TCA TGT GGA CCT CAG TGT CAC AAG GGA ACA CCA CTG CCC ACC TAC GAA GAG GCC AAG CAG     393

 Y  L  S  Y  E  T  L  Y  A  N  G  S  R  T  E  T  R  V  G  I                      102
TAC CTT TCC TAT GAA ACC CTT TAT GCC AAT GGC AGC CGC ACA GAG ACT CGG GTG GGC ATC     453

 Y  I  L  S  N  G  E  G  R  A  R  G  R  D  S  E  A  T  G  R                      122
TAC ATC CTC AGC AAT GGT GAA GGC AGG GCA CGA GGC AGA GAC TCG GAG GCC ACA GGG AGA     513

 S  R  R  K  R  Q  I  Y  G  Y  D  G  R  F  S  I  F  G  K  D                      142
TCT CGC AGG AAG AGG CAG ATT TAT GGC TAC GAT GGC AGG TTT AGC ATT TTT GGG AAG GAC     573

 F  L  L  N  Y  P  F  S  T  S  V  K  L  S  T  G  C  T  G  T                      162
TTC CTG CTC AAT TAT CCT TTC TCA ACA TCG GTG AAG TTG TCT ACT GGC TGC ACT GGC ACC     633

 L  V  A  E  K  H  V  L  T  A  A  H  C  I  H  D  G  K  T  Y                      182
CTG GTG GCA GAG AAG CAC GTC CTC ACT GCT GCC CAC TGC ATA CAC GAT GGG AAA ACC TAT     693

 V  K  G  T  Q  K  L  R  V  G  F  L  K  P  K  Y  K  D  G  A                      202
GTG AAA GGG ACA CAG AAA CTC CGA GTG GGC TTC CTG AAG CCC AAG TAT AAA GAT GGT GCC     753

 E  G  D  N  S  S  S  S  A  M  P  D  K  M  K  F  Q  W  I  R                      222
GAA GGG GAC AAC AGC TCG AGC TCA GCC ATG CCA GAC AAG ATG AAG TTT CAG TGG ATC CGC     813

 V  K  R  T  H  V  P  K  G  W  I  K  G  N  A  N  D  I  G  M                      242
GTG AAA CGC ACC CAT GTG CCC AAG GGG TGG ATC AAG GGC AAT GCC AAT GAC ATC GGC ATG     873

 D  Y  D  Y  A  L  L  E  L  K  K  P  H  K  R  Q  F  M  K  I                      262
GAT TAT GAC TAC GCC CTG CTG GAA CTC AAG AAA CCC CAC AAA AGA CAG TTC ATG AAG ATT     933

 G  V  S  P  P  A  K  Q  L  P  G  G  R  I  H  F  S  G  Y  D                      282
GGT GTG AGT CCT CCA GCG AAG CAG CTC CCA GGG GGC AGG ATC CAC TTC TCT GGT TAT GAC     993

 N  D  R  P  G  N  L  V  Y  R  F  C  D  V  K  D  E  T  Y  D                      302
AAT GAC CGG CCC GGC AAT TTG GTG TAC CGC TTC TGT GAT GTC AAA GAT GAG ACC TAC GAC    1053

 L  L  Y  Q  Q  C  D  A  Q  P  G  A  S  G  S  G  V  Y  V  R                      322
CTT CTC TAC CAG CAG TGT GAC GCC CAG CCC GGG GCC AGT GGT TCA GGG GTC TAT GTG AGG    1113

 M  W  K  R  P  Q  Q  K  W  E  R  K  I  I  G  I  F  S  G  H                      342
ATG TGG AAG AGA CCA CAG CAG AAA TGG GAA AGA AAA ATT ATC GGC ATC TTT TCA GGG CAC    1173

 Q  W  V  D  M  N  G  S  P  Q  D  F  N  V  A  V  R  I  T  P                      362
CAG TGG GTG GAC ATG AAT GGC TCT CCA CAG GAT TTC AAC GTG GCA GTT AGA ATC ACG CCT    1233
```

Fig 1d (1 of 2)

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 L   K   Y   A   Q   I   C   Y   W   I   K   G   N   Y   L   D   C   R   E   G    382
CTT AAA TAT GCC CAG ATT TGC TAT TGG ATT AAA GGA AAC TAC CTA GAT TGC AGG GAG GGG  1293

 *                                                                               383
TGA                                                                             1296

CATGCGTCTTCTTGCCAGCACCAATGGTCTTTTTGCACTCATTGTAGGAGAGGCTAGCTTTTTATCATTGACTCTTGTG 1375

GTGTGAGTCACATAGTATCTTTTACCTAGTATTCTTCAAATGGCAAAAATTATTGGCTATATTATTTTAAAACTGTTGT 1454

GTGCGTTATAGCATTTAAGCAGTCTGAAAGCATACTTTTGCATAGAGACTTTAAAGTATTCGGGTAATAGGGCCTATTT 1533

GACAAGGAAGTTAAACTTTCAGTTTTTGGAGAATTCTAATTTTTGTCTGATCCAAACTTGCTTCAGAGGTTTATATCAA 1612

ATACGTGACACACAGGGAATATGAATTCTTATGTTTGTATATGTATATGTTTTCTTCTGAGAGTCATATATTGATATTT 1691

TTGTAATGTGTGGTTATTATGCTTCCAGATAATGATAGCAAAGTCTTCAATAGGCAATTTATAATGTTTTGGATTCAAA 1770

CATTTACGTAGTAGTCCTTGAAGAGAACAATAATTTATTGGCTATATTGATACCCATATAAGACTGTATCTTACAGTGC 1849

ACAGAATTCCCACGCTGCTTTTAGTTTTGAAAATAAAACTTTCCCTTGTAAAAAAAAAAAAAAAAAAAAAAGGGCGGCCG 1928

ACAGAATTCCCACGCTGCTTTTAGTTTTGAAAATAAAACTTTCCCTTGTAAAAAAAAAAAAAAAAAAAAAAGGGCGGCCG 1928
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                          M  A  P  A  S  R  L  L  A  L  W  A  L  A     14
GTCGACCCACGCGTCCGGGCTC ATG GCG CCG GCG TCG CGG TTG CTC GCG CTC TGG GCG CTG GCG    64

 A  V  A  L  P  G  S  G  A  E  G  D  G  G  W  R  P  G  G  P     34
GCT GTG GCT CTA CCC GGC TCC GGG GCG GAG GGC GAC GGC GGG TGG CGC CCG GGC GGG CCG   124

 G  A  V  A  E  E  E  R  C  T  V  E  R  R  A  D  L  T  Y  A     54
GGG GCC GTG GCG GAG GAG GAG CGC TGC ACG GTG GAG CGT CGG GCC GAC CTC ACC TAC GCG   184

 E  F  V  Q  Q  Y  A  F  V  R  P  V  I  L  Q  G  L  T  D  N     74
GAG TTC GTG CAG CAG TAC GCC TTC GTC AGG CCC GTC ATC CTG CAG GGA CTC ACG GAC AAC   244

 S  R  F  R  A  L  C  S  R  D  R  L  L  A  S  F  G  D  R  V     94
TCG AGG TTC CGG GCC CTG TGC TCC CGC GAC AGG TTG CTG GCT TCG TTT GGG GAC AGA GTG   304

 V  R  L  S  T  A  N  T  Y  S  Y  H  K  V  D  L  P  F  Q  E    114
GTC CGG CTG AGC ACC GCC AAC ACC TAC TCC TAC CAC AAA GTG GAC TTG CCC TTC CAG GAG   364

 Y  V  E  Q  L  L  H  P  Q  D  P  T  S  L  G  N  D  T  L  Y    134
TAT GTG GAG CAG CTG CTG CAC CCC CAG GAC CCC ACC TCC CTG GGC AAT GAC ACC CTG TAC   424

 F  F  G  D  N  N  F  T  E  W  A  S  L  F  R  H  Y  S  P  P    154
TTC TTC GGG GAC AAC AAC TTC ACC GAG TGG GCC TCT CTC TTT CGG CAC TAC TCC CCA CCC   484

 P  F  G  L  L  G  T  A  P  A  Y  S  F  G  I  A  G  A  G  S    174
CCA TTT GGC CTG CTG GGA ACC GCT CCA GCT TAC AGC TTT GGA ATC GCA GGA GCT GGC TCG   544

 G  V  P  F  H  W  H  G  P  G  Y  S  E  V  I  Y  G  R  K  R    194
GGG GTG CCC TTC CAC TGG CAT GGA CCC GGG TAC TCA GAA GTG ATC TAC GGT CGT AAG CGC   604

 W  F  L  Y  P  P  E  K  T  P  E  F  H  P  N  K  T  T  L  A    214
TGG TTC CTT TAC CCA CCT GAG AAG ACG CCA GAG TTC CAC CCC AAC AAG ACC ACG CTG GCC   664

 W  L  R  D  T  Y  P  A  L  P  P  S  A  R  P  L  E  C  T  I    234
TGG CTC CGG GAC ACA TAC CCA GCC CTG CCA CCG TCT GCA CGG CCC CTG GAG TGT ACC ATC   724

 R  A  G  E  V  L  Y  F  P  D  R  W  W  H  A  T  L  N  L  D    254
CGG GCT GGT GAG GTG CTG TAC TTC CCC GAC CGC TGG TGG CAT GCT ACG CTC AAC CTT GAC   784

 T  S  V  F  I  S  T  F  L  G  *                                265
ACC AGC GTC TTC ATC TCC ACC TTC CTC GGC TAG                      817

CCAAAACAGCTGGCAGGACTGCCGGTCACACACCAGCACGTCCCACCTCGTGCTCACGGATTTTATTACACAGATAGTG  896

GCGGCAATGGCCTCAGCCCAGCCCACCCTCACCTGCTTTTCCAGCCCACAAAGGGGGACGATCACGGCCCAGCAAAAGC  975

GATGCTGAGAGGGGAAACAGTCCAGAGTCCAACAGCAGAACTTGGGGGAAGCGGTCGGGGTGGCCAGGAACATAAACTA 1054

TGTATAGGGGCCGGGGGCTTCTGCCCAGGGCTCCCCTGGACCAGGACGCCAGGTAGGGCAGGGAACCTCAGTAGTCCTC 1133

CACCCAGCCATTCTCAGAGATGAATGCGTCAATAACCTCCTTCATAGCCAAGTTGGGGATGAGCTGTTCCTGGGTCAGG 1212

GGGCTCCGGGTCACGGGGTCAAAATGACCCACACGCTGCAGTGACAAGAAGGGCAGAGGGCAGTCATGGGGCCCAGGAC 1291

CATGCCACTGGCCCTGCTCCCCCAGCCGCAGGCCTCACCTGCAGGTGCTCCTCGATGTCCTTGCGGTCGTAGGTGATGC 1370

CACTGGGCGTGATGCACGGCTCCCGCATCAGCTCAAAGCTGATCTTGCCACACAGGTAGTCGGGGATGTCTCGCTTCTG 1449
```

FIG 15 (1 OF 2)

TGGCACAGGGGCACACGGTCAGAGGCTGAAAAGGGGCACTGCACGAGCACCTGCCAGCCATCGGCAGCAAGCGACACAC 1528

ACTCACCTTCCTCTTCTCATCCACCTGAGAAAAAAAGCTCGTCCATGTCCGCCATGTACTTGTCCTGTGAAGAGTTGAGT 1607

GCTGTGCTTGGGGGAGACACCCCACCTCCCTCCTCCATGGGGCACAGACCCAACACAAGGCGGGGATGCTCCCACGCCA 1686

CGTGCACACACACAGACCCACATGTGGGTGGGGGGCACCCTCACGTGCTTGGCCTCAATGCAGGCCTGCTGGGCCCGGA 1765

CGTGGCTGTCGTCCTCATCACCCTCGTGGTTTCGCTGGCACTCTTCCAGCTCCCTGGGGGTTGACCAGGAGCCGGTCAG 1844

AGATGGACCTGGCCAGATGTCTGACCACACCCCAATCTCAGAGCTAACATCCACACTTCCCCACATTTCCTGCTTGCCA 1923

GTAAAGCCTTCGATAAACAAAAAAAAAAAAAAAAAAAAAGGGCGGCCG 1970

FIG 15 (2 OF 2)

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                                M  A  A  A  G  R  R  G  L  L  L  L  F  V     14
GTCGACCCACGCGTCCGGTTC ATG GCG GCG GCT GGG CGG CGC GGT CTG CTT TTG CTC TTT GTA     63

 L  W  M  M  V  T  V  I  L  P  A  S  G  E  G  G  W  K  Q  N     34
CTA TGG ATG ATG GTG ACT GTG ATT CTG CCT GCC TCT GGC GAA GGG GGA TGG AAA CAG AAT  123

 G  L  G  I  A  A  A  V  M  E  E  E  R  C  T  V  E  R  R  A     54
GGG CTG GGA ATT GCA GCA GCA GTA ATG GAG GAG GAG CGT TGC ACA GTG GAG CGT CGG GCA  183

 H  I  T  Y  S  E  F  M  Q  H  Y  A  F  L  K  P  V  I  L  Q     74
CAC ATC ACG TAC TCC GAA TTC ATG CAG CAC TAT GCC TTC CTC AAG CCC GTC ATC TTG CAA  243

 G  L  T  D  N  S  K  F  R  A  L  C  S  R  E  N  L  L  A  S     94
GGA CTC ACG GAC AAC TCG AAG TTC CGG GCC CTG TGT TCC CGG GAA AAC CTG CTA GCC TCG  303

 F  G  D  N  I  V  R  L  S  T  A  N  T  Y  S  Y  Q  K  V  D    114
TTC GGG GAC AAC ATT GTT CGC TTG AGT ACA GCC AAC ACC TAC TCC TAC CAG AAA GTG GAC  363

 L  P  F  Q  E  Y  V  E  Q  L  L  Q  P  Q  D  P  A  S  L  G    134
CTG CCC TTC CAG GAA TAT GTG GAA CAG CTG CTG CAG CCC CAG GAT CCT GCA TCC CTA GGC  423

 N  D  T  L  Y  F  F  G  D  N  N  F  T  E  W  A  S  L  F  Q    154
AAT GAC ACC CTG TAC TTT TTT GGA GAC AAC AAC TTC ACT GAG TGG GCA TCC CTC TTC CAG  483

 H  Y  S  P  P  P  F  R  L  L  G  T  T  P  A  Y  S  F  G  I    174
CAC TAC TCT CCG CCA CCA TTC CGT CTC CTG GGA ACC ACC CCT GCT TAC AGC TTT GGA ATT  543

 A  G  A  G  S  G  V  P  F  H  W  H  G  P  G  F  S  E  V  I    194
GCA GGA GCT GGA TCT GGG GTA CCC TTC CAC TGG CAT GGG CCT GGT TTC TCA GAG GTT ATC  603

 Y  G  R  K  R  W  F  L  Y  P  P  E  K  T  P  E  F  H  P  N    214
TAT GGT CGG AAG CGC TGG TTC CTC TAC CCT CCT GAG AAG ACA CCT GAG TTC CAC CCT AAC  663

 K  T  T  L  A  W  L  L  E  I  Y  P  S  L  A  L  S  A  R  P    234
AAG ACC ACA TTG GCC TGG CTG CTG GAA ATA TAC CCA TCT CTA GCC CTG TCA GCA CGG CCT  723

 L  E  C  T  I  Q  A  G  E  V  L  Y  F  P  D  R  W  W  H  A    254
CTA GAA TGT ACC ATC CAG GCT GGT GAA GTA CTG TAT TTT CCT GAT CGG TGG TGG CAT GCC  783

 T  L  N  L  D  T  S  V  F  I  S  T  F  L  G  •                270
ACA CTC AAT CTG GAC ACC AGT GTC TTC ATT TCT ACC TTC CTT GGC TAG                  831

CCAGACAGGCAACTGGCAAGCCCACTGCACCAGCACATGCCAATGTAGTGCTCACAGACTTTATTACAGGACAGTGGCA  910

GCAGCAGCAACCTCAGCCCACCCTCACCCACTCTCCAGCCCAGAAGGGGGACAAGGGAGGCTCATGGTCCAGCAAGGGG  989

TATGCTGAGAAGGGGAGCAGTTCAGAACCCATCAGCAGGGCCGATGGGGGCAGGCCCAGGGACACAAACTATACAGGGA 1068

CTGGAGCTTCCGTCTCCAGATCCTCCTGGGCCAGGGTGCCAGGCAGGACATGGGGCCTCAATAGTCCTCTACCCAGCCG 1147

TTCTCAGAGATGAAAGCGTCAATGACTTCCTTCATGGCCAAGTTGGGGATGAGCTGTTCCTGGGTCAAAGGGCTCCGGG 1226

TCACAGGGTCAAAGTGGCCCACACGCTGCAACAGAGTCAAGAGTGTTCAATGGCCTGAGTATACCGATCCGGGTACCAA 1305

GGCTCTCCATGGCCCGGTCTCCATGGGCCCTCCTTACCTGCAGGTGCTCCTCAATGTCCTTGCGGTCATAGGTGATACC 1384

ACTGGGTGTAATGCAGGGTTCCCGCATCAGCTCAAAGCTAATCTTGCCACACAAGTAGTCAGGGATATCTCGCTTCTAT 1463
```

Fig 1G (1 of 2)

AGCACAAGGGGAAAATGTCTAGAACTGGAGGGGGCTGTGGGGGTCACCATACCAGCAGCAGCCGATGAGCTTCCGGGGG 1542

TCCTCACCTTTCTTTTCTCGTCCACCTGAGAGAAGAGCTCATCCATATCTGCCATGTATTTATCCTGCAGAGTTGAGTG 1621

CCATGTGTGGGCAACTCCTGTCTCCACACAGACACACACACTCTGTCCACCAGGGCACTCATGTCATGCATGGGCCAAC 1700

AGATCCACCAAAGGCTGGGGCACTTTTCATGCCACACACAAACACACACACAATGACCCACATGTGGACTAGGGGCACC 1779

CTCACGTGCTTGGCCTCAATGCAGGCCTGCTGGGCCCGGATGTGGCCATCATCTTCATGACCCTCGTGGTTCCGCTGAC 1858

ACTCCTCCAGTTCCCTGAGGGTTAACCAGAAGCTAGTTGGTGATGGCCCTGACCAGGAAATCACAGAGCCCGCCCCATC 1937

TCAGGCCTCTTTCCTCCTGGGCTTCCCATGTACCGGTTGTTGTCCTTCAATAAAAACACTTGTGCTGGTGACTCAGTGT 2016

CTGCTGGGGGAGGGACCCACCTCTCTCGCTCAGCAGCAATGAGCCTGGTGAGATATGAATGCAAAAAAAAAAAAAAAGG 2095

GCGGCCG
2102

FIG 1C (2 OF 2)

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                                                                M  D  N  R  F  A        6
CACGCGTCCGGCTGGCGGAGCAGGAGGATGGGCGAGCAGTCTGAATGCCAGA ATG GAT AAC CGT TTT GCT       70

 T  A  F  V  I  A  C  V  L  S  L  I  S  T  I  Y  M  A  A  S    26
ACA GCA TTT GTA ATT GCT TGT GTG CTT AGC CTC ATT TCC ACC ATC TAC ATG GCA GCC TCC  130

 I  G  T  D  F  W  Y  E  Y  R  S  P  V  Q  E  N  S  S  D  L    46
ATT GGC ACA GAC TTC TGG TAT GAA TAT CGA AGT CCA GTT CAA GAA AAT TCC AGT GAT TTG  190

 N  K  S  I  W  D  E  F  I  S  D  E  A  D  E  K  T  Y  N  D    66
AAT AAA AGC ATC TGG GAT GAA TTC ATT AGT GAT GAG GCA GAT GAA AAG ACT TAT AAT GAT  250

 A  L  F  R  Y  N  G  T  V  G  L  W  R  R  C  I  T  I  P  K    86
GCA CTT TTT CGA TAC AAT GGC ACA GTG GGA TTG TGG AGA CGG TGT ATC ACC ATA CCC AAA  310

 N  M  H  W  Y  S  P  P  E  R  T  E  S  F  D  V  V  T  K  C   106
AAC ATG CAT TGG TAT AGC CCA CCA GAA AGG ACA GAG TCA TTT GAT GTG GTC ACA AAA TGT  370

 V  S  F  T  L  T  E  Q  F  M  E  K  F  V  D  P  G  N  H  N   126
GTG AGT TTC ACA CTA ACT GAG CAG TTC ATG GAG AAA TTT GTT GAT CCC GGA AAC CAC AAT  430

 S  G  I  D  L  L  R  T  Y  L  W  R  C  Q  F  L  L  P  F  V   146
AGC GGG ATT GAT CTC CTT AGG ACC TAT CTT TGG CGT TGC CAG TTC CTT TTA CCT TTT GTG  490

 S  L  G  L  M  C  F  G  A  L  I  G  L  C  A  C  I  C  R  S   166
AGT TTA GGT TTG ATG TGC TTT GGG GCT TTG ATC GGA CTT TGT GCT TGC ATT TGC CGA AGC  550

 L  Y  P  T  I  A  T  G  I  L  H  L  L  A  G  N  Y  S  D  S   186
TTA TAT CCC ACC ATT GCC ACG GGC ATT CTC CAT CTC CTT GCA GGA AAT TAC TCA GAT TCT  610

 W  L  H  E  *                                                  191
TGG CTC CAT GAA TAA                                            625

TTTTAATGATCTTCTACATTATCCTTGATAATTACTCATTTCTCAATAATCTTTTAATTTCATCCCATGACTCTGAGGA  704

TAGCTTCCAAGCTCTTTAAATGGCCTTACAAACTCATTGGCAAGTTCTATACTTCAGGCACACTGACCTTTTAGTTTTT  783

CCAGTGGGCCATGCCTATGGTAGTTTAAAAACATGGCCTTAAAATCCTTCGATCAATCTTGCATTGAGATTCCCATCCC  862

CTTGAATCTAGGCTGGCTTGTGATGGTTTTGACCAATAGAGTGTGCCTGAAATGACACTCTTCTCATGAGGTCCTAAAG  941

ATCATGTGTCCTTAAACCAGTTCTCTTGGAACACTCAGTCTTAGAACATTCCCTCTCCAAACCCAGATACCATGCTGTG 1020

AAGTCCAGGCCACATGGAGGTGTCCTGTGTAGATGCTCCAGCTGAAATCCCAAGCTAAGCTCCCAACTGACAGCCAACA 1099

TCATTTCCAGCCATGTGTGGGAGCCATCCTGGATGTCCAGCCTTAACAAGCCTTCAGAGGACTTCAGCCACAGCTATTA 1178

TCTTACTACATCCTTGTGAGACTCTAATAAAGAACCAACTAGCTGAGCCCAATCAACCTATGGAACTGATAGAAATAAA 1257

ATGAATTGTTGTTTTGTGCCGCTAAAAAAAAAAAAAAAAAAAAAAAAAAAA                              1308
```

Fig. 1

```
                                                                  M   D   N   R      4
AATTCGGMWCMKKKGVVGGVVGCCGGTGGAGTGAGAGGATGGGCGAGCAGTCTGAATGCCAGA ATG GAT AAC CGT   75

 F   A   T   A   F   V   I   A   C   V   L   S   L   I   S   T   I   Y   M   A    24
TTT GCT ACT GCG TTT GTG ATT GCT TGT GTG CTT AGT CTG ATT TCC ACC ATC TAC ATG GCG  135

 A   S   I   G   T   D   F   W   Y   E   Y   R   S   P   I   Q   E   N   S   S    44
GCC TCC ATA GGC ACG GAC TTC TGG TAT GAG TAT CGA AGT CCC ATT CAA GAG AAT TCA AGT  195

 D   S   N   K   I   A   W   E   D   F   L   G   D   E   A   D   E   K   T   Y    64
GAC TCG AAT AAA ATC GCC TGG GAA GAT TTC CTC GGT GAC GAG GCG GAT GAG AAG ACT TAC  255

 N   D   V   L   F   R   Y   N   G   S   L   G   L   W   R   R   C   I   T   I    84
AAC GAT GTT CTG TTC CGA TAC AAC GGC AGC TTG GGG CTG TGG AGA CGG TGC ATC ACC ATA  315

 P   K   N   T   H   W   Y   A   P   P   E   R   T   E   S   F   D   V   V   T   104
CCC AAA AAC ACT CAC TGG TAT GCG CCA CCG GAA AGG ACA GAG TCA TTT GAT GTG GTT ACC  375

 K   C   M   S   F   T   L   N   E   Q   F   M   E   K   Y   V   D   P   G   N   124
AAA TGC ATG AGT TTC ACA CTA AAC GAG CAG TTC ATG GAG AAG TAT GTG GAC CCC GGC AAC  435

 H   N   S   G   I   D   L   L   R   T   Y   L   W   R   C   Q   F   L   L   P   144
CAC AAT AGC GGC ATC GAC CTG CTT CGC ACC TAC CTG TGG CGC TGC CAG TTC CTT TTA CCC  495

 F   V   S   L   G   L   M   C   F   G   A   L   I   G   L   C   A   C   I   C   164
TTC GTC AGC TTG GGC TTG ATG TGC TTT GGG GCG TTG ATT GGC CTC TGT GCC TGT ATC TGC  555

 R   S   L   Y   P   T   L   A   T   G   I   L   H   L   L   A   G   L   C   T   184
CGC AGC CTG TAT CCC ACC CTC GCC ACT GGC ATT CTC CAT CTC CTT GCA GGT CTG TGC ACA  615

 L   G   S   V   S   C   Y   V   A   G   I   E   L   L   H   Q   K   V   E   L   204
CTG GGC TCC GTG AGT TGC TAT GTT GCC GGC ATT GAA CTC TTA CAT CAG AAA GTA GAG CTG  675

 P   K   D   V   S   G   E   F   G   W   S   F   C   L   A   C   V   S   A   P   224
CCC AAG GAT GTA TCT GGA GAA TTT GGA TGG TCC TTC TGC CTG GCC TGC GTC TCG GCT CCC  735

 L   Q   F   M   A   A   A   L   F   I   W   A   A   H   T   N   R   K   E   Y   244
TTA CAG TTC ATG GCG GCC GCT CTC TTC ATC TGG GCT GCC CAC ACC AAC CGG AAA GAG TAC  795

 T   L   M   K   A   Y   R   V   A   *                                          254
ACC TTA ATG AAG GCT TAT CGT GTG GCA TGA                                         825

AGGGAGGCTGCCTGCTTAATGATTAATATTTTTCATACATTTTTTT                                   871
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FIG. 1E

HUMAN TANGO 215

Input file tag215; Output File tag215.pat Sequence length 2747

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                                        M  E  L  G  C  W  T  Q  L  G      10
TCCCCAGTAGACGCTCCGGCACCAGCCGCGGCAAGG ATG GAG CTG GGT TGC TGG ACG CAG TTG GGG      66

 L  T  F  L  Q  L  L  L  I  S  S  L  P  R  E  Y  T  V  I  N      30
CTC ACT TTT CTT CAG CTC CTT CTC ATC TCG TCC TTG CCA AGA GAG TAC ACA GTC ATT AAT   126

 E  A  C  P  G  A  E  W  N  I  M  C  R  E  C  C  E  Y  D  Q      50
GAA GCC TGC CCT GGA GCA GAG TGG AAT ATC ATG TGT CGG GAG TGC TGT GAA TAT GAT CAG   186

 I  E  C  V  C  P  G  K  R  E  V  V  G  Y  T  I  P  C  C  R      70
ATT GAG TGC GTC TGC CCC GGA AAG AGG GAA GTC GTG GGT TAT ACC ATC CCT TGC TGC AGG   246

 N  E  E  N  E  C  D  S  C  L  I  H  P  G  C  T  I  F  E  N      90
AAT GAG GAG AAT GAG TGT GAC TCC TGC CTG ATC CAC CCA GGT TGT ACC ATC TTT GAA AAC   306

 C  K  S  C  R  N  G  S  W  G  G  T  L  D  D  F  Y  V  K  G     110
TGC AAG AGC TGC CGA AAT GGC TCA TGG GGG GGT ACC TTG GAT GAC TTC TAT GTG AAG GGG   366

 F  Y  C  A  E  C  R  A  G  W  Y  G  G  D  C  M  R  C  G  Q     130
TTC TAC TGT GCA GAG TGC CGA GCA GGC TGG TAC GGA GGA GAC TGC ATG CGA TGT GGC CAG   426

 V  L  R  A  P  K  G  Q  I  L  L  E  S  Y  P  L  N  A  H  C     150
GTT CTG CGA GCC CCA AAG GGT CAG ATT TTG TTG GAA AGC TAT CCC CTA AAT GCT CAC TGT   486

 E  W  T  I  H  A  K  P  G  F  V  I  Q  L  R  F  V  M  L  S     170
GAA TGG ACC ATT CAT GCT AAA CCT GGG TTT GTC ATC CAA CTA AGA TTT GTC ATG TTG AGC   546

 L  E  F  D  Y  M  C  Q  Y  D  Y  V  E  V  R  D  G  D  N  R     190
CTG GAG TTT GAC TAC ATG TGC CAG TAT GAC TAT GTT GAG GTT CGT GAT GGA GAC AAC CGC   606

 D  G  Q  I  I  K  R  V  C  G  N  E  R  P  A  P  I  Q  S  I     210
GAT GGC CAG ATC ATC AAG CGT GTC TGT GGC AAC GAG CGG CCA GCT CCT ATC CAG AGC ATA   666

 G  S  S  L  H  V  L  F  H  S  D  G  S  K  N  F  D  G  F  H     230
GGA TCC TCA CTC CAC GTC CTC TTC CAC TCC GAT GGC TCC AAG AAT TTT GAC GGT TTC CAT   726

 A  I  Y  E  E  I  T  A  C  S  S  S  P  C  F  H  D  G  T  C     250
GCC ATT TAT GAG GAG ATC ACA GCA TGC TCC TCA TCC CCT TGT TTC CAT GAC GGC ACG TGC   786

 V  L  D  K  A  G  S  Y  K  C  A  C  L  A  G  Y  T  G  Q  R     270
GTC CTT GAC AAG GCT GGA TCT TAC AAG TGT GCC TGC TTG GCA GGC TAT ACT GGG CAG CGC   846

 C  E  N  L  L  E  E  R  N  C  S  D  P  G  G  P  I  N  G  Y     290
TGT GAA AAT CTC CTT GAA GAA AGA AAC TGC TCA GAC CCT GGG GGC CCG ATC AAT GGG TAC   906

 Q  K  I  T  G  G  P  G  L  I  N  G  R  H  A  K  I  G  T  V     310
CAG AAA ATA ACA GGG GGC CCT GGG CTT ATC AAC GGA CGC CAT GCT AAA ATT GGC ACC GTT   966

 V  S  F  F  C  Y  N  S  Y  V  L  S  G  N  E  K  R  T  C  Q     330
GTG TCT TTC TTT TGT TAC AAC TCC TAT GTT CTT AGT GGC AAT GAG AAA AGA ACT TGC CAG  1026

 Q  N  G  E  W  S  G  K  Q  P  I  C  I  K  A  C  R  E  P  K     350
CAG AAT GGA GAG TGG TCA GGG AAA CAG CCC ATC TGC ATA AAA GCC TGC CGA GAA CCA AAG  1086

 I  S  D  L  V  R  R  R  V  L  P  M  Q  V  Q  S  R  E  T  P     370
ATT TCA GAC CTG GTG AGA AGG AGA GTT CTT CCG ATG CAG GTT CAG TCA AGG GAG ACA CCA  1146
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FIG 19 (1 OF 2)

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 L  H  Q  L  Y  S  A  A  F  S  K  Q  K  L  Q  S  A  P  T  K   390
TTA CAC CAG CTA TAC TCA GCG GCC TTC AGC AAG CAG AAA CTG CAG AGT GCC CCT ACC AAG  1206

 K  P  A  L  P  F  G  D  L  P  M  G  Y  Q  H  L  H  T  Q  L   410
AAG CCA GCC CTT CCC TTT GGA GAT CTG CCC ATG GGA TAC CAA CAT CTG CAT ACC CAG CTC  1266

 Q  Y  E  C  I  S  P  F  Y  R  R  L  G  S  S  R  R  T  C  L   430
CAG TAT GAG TGC ATC TCA CCC TTC TAC CGC CGC CTG GGC AGC AGC AGG AGG ACA TGT CTG  1326

 R  T  G  K  W  S  G  R  A  P  S  C  I  P  I  C  G  K  I  E   450
AGG ACT GGG AAG TGG AGT GGG CGG GCA CCA TCC TGC ATC CCT ATC TGC GGG AAA ATT GAG  1386

 N  I  T  A  P  K  T  Q  G  L  R  W  P  W  Q  A  A  I  Y  R   470
AAC ATC ACT GCT CCA AAG ACC CAA GGG TTG CGC TGG CCG TGG CAG GCA GCC ATC TAC AGG  1446

 R  T  S  G  V  H  D  G  S  L  H  K  G  A  W  F  L  V  C  S   490
AGG ACC AGC GGG GTG CAT GAC GGC AGC CTA CAC AAG GGA GCG TGG TTC CTA GTC TGC AGC  1506

 G  A  L  V  N  E  R  T  V  V  V  A  A  H  C  V  T  D  L  G   510
GGT GCC CTG GTG AAT GAG CGC ACT GTG GTG GTG GCT GCC CAC TGT GTT ACT GAC CTG GGG  1566

 K  V  T  M  I  K  T  A  D  L  K  V  V  L  G  K  F  Y  R  D   530
AAG GTC ACC ATG ATC AAG ACA GCA GAC CTG AAA GTT GTT TTG GGG AAA TTC TAC CGG GAT  1626

 D  D  R  D  E  K  T  I  Q  S  L  Q  I  S  A  I  I  L  H  P   550
GAT GAC CGG GAT GAG AAG ACC ATC CAG AGC CTA CAG ATT TCT GCT ATC ATT CTG CAT CCC  1686

 N  Y  D  P  I  L  L  D  A  D  I  A  I  L  K  L  L  D  K  A   570
AAC TAT GAC CCC ATC CTG CTT GAT GCT GAC ATC GCC ATC CTG AAG CTC CTA GAC AAG GCC  1746

 R  I  S  T  R  V  Q  P  I  C  L  A  A  S  R  D  L  S  T  S   590
CGT ATC AGC ACC CGA GTC CAG CCC ATC TGC CTC GCT GCC AGT CGG GAT CTC AGC ACT TCC  1806

 F  Q  E  S  H  I  T  V  A  G  W  N  V  L  A  D  V  R  S  P   610
TTC CAG GAG TCC CAC ATC ACT GTG GCT GGC TGG AAT GTC CTG GCA GAC GTG AGG AGC CCT  1866

 G  F  K  N  D  T  L  R  S  G  V  V  S  V  V  D  S  L  L  C   630
GGC TTC AAG AAC GAC ACA CTG CGC TCT GGG GTG GTC AGT GTG GTG GAC TCG CTG CTG TGT  1926

 E  E  Q  H  E  D  H  G  I  P  V  S  V  T  D  N  M  F  C  A   650
GAG GAG CAG CAT GAG GAC CAT GGC ATC CCA GTG AGT GTC ACT GAT AAC ATG TTC TGT GCC  1986

 S  W  E  P  T  A  P  S  D  I  C  T  A  E  T  G  G  I  A  A   670
AGC TGG GAA CCC ACT GCC CCT TCT GAT ATC TGC ACT GCA GAG ACA GGA GGC ATC GCG GCT  2046

 V  S  F  P  G  R  A  S  P  E  P  R  W  H  L  M  G  L  V  S   690
GTG TCC TTC CCG GGA CGA GCA TCT CCT GAG CCA CGC TGG CAT CTG ATG GGA CTG GTC AGC  2106

 W  S  Y  D  K  T  C  S  H  R  L  S  T  A  F  T  K  V  L  P   710
TGG AGC TAT GAT AAA ACA TGC AGC CAC AGG CTC TCC ACT GCC TTC ACC AAG GTG CTG CCT  2166

 F  K  D  W  I  E  R  N  M  K  *                               721
TTT AAA GAC TGG ATT GAA AGA AAT ATG AAA TGA                     2199

ACCATGCTCATGCACTCCTTGAGAAGTGTTTCTGTATATCCGTCTGTACGTGTGTCATTGCGTGAANCAGTGTGGGCCT  2278

GAAGTGTGATTTGGCCTGTGAACTTGGCTGTGCCAGGGCTTCTGACTTCAGGGACAAAACTCAGTGAAGGGTGAGTAGA  2357

CCTCCATTGCTGGTAGGCTGATGCCVCGTCCACTACTAGGACAGCCAATTGGAAGATGCCAGGGCTTGCAAGAAGTAAG  2436
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FIG 19 (2 of 3)

TTTCTTCAAAGAAGACCATATACAAAACCTCTCCACTCCACTGACCTGGTGGTCTTCCCCAACTTTCAGTTATACGAAT 2515

GCCATCAGCTTGACCAGGGAAGATCTGGGCTTCATGAGGCCCCTTTTGAGGCTCTCAAGTTCTAGAGAGCTGCCTGTGG 2594

GACAGCCCAGGGCAGCAGAGCTGGGATGTGGTGCATGCCTTTGTGTACATGGCCACAGTACAGTCTGGTCCTTTTCCTT 2673

CCCCATCTCTTGTACACATTTTAATAAAATAAGGGTTGGCTTCTGAACTACAAAAAAAAAAAAAAAAAAAAAAAA 2747

FIG 17 (3 of 3)

```
GTCGACCCACGCGTCCGGCGGCTAGGCCCGCGTGCGCTGGAGACCTCCGCGCTGGCCCCCGCGAGCCTCCTGCCCTGGC 79

                                        M  G  G  P  R  G  A  G  W  V  A  A      12
CCGGCGCTGCGGCTCTGCCGCGGCGGCAGC ATG GGT GGC CCC CGG GGC GCG GGC TGG GTG GCG GCG    145

 G  L  L  L  G  A  G  A  C  Y  C  I  Y  R  L  T  R  G  R  R      32
GGC CTG CTG CTC GGC GCG GGC GCC TGC TAC TGC ATT TAC AGG CTG ACC CGG GGT CGG CGG   205

 R  G  D  R  E  L  G  I  R  S  S  K  S  A  G  A  L  E  E  G      52
CGG GGC GAC CGC GAG CTC GGG ATA CGC TCT TCG AAG TCC GCA GGT GCC CTG GAA GAA GGG   265

 T  S  E  G  Q  L  C  G  R  S  A  R  P  Q  T  G  G  T  W  E      72
ACG TCA GAG GGT CAG TTG TGC GGG CGC TCG GCC CGG CCT CAG ACG GGA GGT ACC TGG GAG   325

 S  Q  W  S  K  T  S  Q  P  E  D  L  T  D  G  S  Y  D  D  V      92
TCA CAG TGG TCC AAG ACC TCG CAG CCT GAA GAC TTA ACT GAT GGT TCA TAT GAT GAT GTT   385

 L  N  A  E  Q  L  Q  K  L  L  Y  L  L  E  S  T  E  D  P  V     112
CTA AAT GCT GAA CAA CTT CAG AAA CTC CTT TAC CTG CTG GAG TCA ACG GAG GAT CCT GTA   445

 I  I  E  R  A  L  I  T  L  G  N  N  A  A  F  S  V  N  Q  A     132
ATT ATT GAA AGA GCT TTG ATT ACT TTG GGT AAC AAT GCA GCC TTT TCA GTT AAC CAA GCT   505

 I  I  R  E  L  G  G  I  P  I  V  A  N  K  I  N  H  S  N  Q     152
ATT ATT CGT GAA TTG GGT GGT ATT CCA ATT GTT GCA AAC AAA ATC AAC CAT TCC AAC CAG   565

 S  I  K  E  K  A  L  N  A  L  N  N  L  S  V  N  V  E  N  Q     172
AGT ATT AAA GAG AAA GCT TTA AAT GCA CTA AAT AAC CTG AGT GTG AAT GTT GAA AAT CAA   625

 I  K  I  K  I  Y  I  S  Q  V  C  E  D  V  F  S  G  P  L  N     192
ATC AAG ATA AAG ATA TAC ATC AGT CAA GTA TGT GAG GAT GTC TTC TCT GGT CCT CTG AAC   685

 S  A  V  Q  L  A  G  L  T  L  L  T  N  M  T  V  T  N  D  H     212
TCT GCT GTG CAG CTG GCT GGA CTG ACA TTG TTG ACA AAC ATG ACT GTT ACC AAT GAC CAC   745

 Q  H  M  L  H  S  Y  I  T  D  L  F  Q  V  L  L  T  G  N  G     232
CAG CAC ATG CTT CAC AGT TAC ATT ACA GAC CTG TTC CAG GTG TTA CTT ACT GGA AAT GGA   805

 N  T  K  V  Q  V  L  K  L  L  L  N  L  S  E  N  P  A  M  T     252
AAC ACG AAG GTG CAA GTT TTG AAA CTG CTT TTG AAT TTG TCT GAA AAT CCA GCC ATG ACA   865

 E  G  L  L  R  A  Q  V  D  S  S  F  L  S  L  Y  D  S  H  V     272
GAA GGA CTT CTC CGT GCC CAA GTG GAT TCA TCA TTC CTT TCC CTT TAT GAC AGC CAC GTA   925

 A  K  E  I  L  L  R  V  L  T  L  F  Q  N  I  K  N  C  L  K     292
GCA AAG GAG ATT CTT CTT CGA GTA CTT ACG CTA TTT CAG AAT ATA AAG AAC TGC CTC AAA   985

 I  E  G  H  L  A  V  Q  P  T  F  T  E  G  S  L  F  F  L  L     312
ATA GAA GGC CAT TTA GCT GTG CAG CCT ACT TTC ACT GAA GGT TCA TTG TTT TTC CTG TTA  1045

 H  G  E  E  C  A  Q  K  I  R  A  L  V  D  H  H  D  A  E  V     332
CAT GGA GAA GAA TGT GCC CAG AAA ATA AGA GCT TTA GTT GAT CAC CAT GAT GCA GAG GTG  1105

 K  E  K  V  V  T  I  I  P  K  I  *                             344
AAG GAA AAG GTT GTA ACA ATA ATA CCC AAA ATC TGA                  1141

TTGGTCATATTTTTCCAAAGAGTAATGCAGTCTGGATATAAATGTATTTTCTGTCTTCCTTATAAGGGGATTCTCCCAG 1220
```

FIG 20 (1 of 2)

CTGCTAAATTTAAACAGTAAATATCACATTTTGTCATTAACACAGCTATAACTTGCCGTGGTTCTCAGATTTATTTTGG 1299

ACTATTTTGATGCCAAGTGAATATAAGAGCTTGTACTGAAACCATTTATTTCTTTCTATTTTGCTATTTGCAAATGCTT 1378

GTTATCTTCCCTACATGAAGTGGCAGTAACCTTTTTCACATTTAAGCTACCCTTCTACCTTTTGAAGTGATTTGCAGTT 1457

ACTCATCTGAGACAGCATCAGTATTTGACTAAATCATTGTTTCACAACTGAATAGTCTTGTTCTTTTAGTAGCAATGAA 1536

ATCCTAAGCTCTTGAGGCCATTCACCTGCCAACCTGACCATACTGCTTTCAAAAGTCTTTTCTCATCAGTAGAATCTAT 1615

TTTGGTCACTTCTAGTCAATGAAAAATGTAAACTTTTAGGAGAGAATGTTTCCTAGGACTCACCCACTCCATTCAATGT 1694

TACATATAAAATAGTGTGATCAATCACAATGTCCATCTTTAGACAGTTGGTTAAATAAATTATCTGGTCTTTGAAAAGA 1773

CCGTGCTGGGCGCGGTGGCTCTTGCCTGTAATCCCAGCACTTTGGGAGGCTGAGGCGGGCAGATCACCTGAGATCGGGA 1852

GTTTGAGACCAAGCCTGACCAATATGGAGAAACCCTGTCTCTACTAAGAATACAAAATTAGCTGGGCATGGTGGTGCAT 1931

GCCTGTAATCCCAGCTACTTGGGAGGCCGAGGCAGGAGAATTGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGGTGAG 2010

ATAGCGCCATTGCACTCCAGCCTGGGCAACAAGAGCAAAACTCTGTCTCAAAAAAAAAAAAAAAAATGATGGAGCTCCGAA 2089

TGTGCTTAAGTGGAAAGATATCTATGAAATATGGTGGTTTTTTAAAACACAAAAATTATAGAATATGGGATCCCGTGTG 2168

TGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTTTGAATGAAAAATGCTTATGTATTGACAGAACACTT 2247

CTAGAATGATACCCAAACTCCTGGAGTGGGAGTGGGGAATGCCTTCTACGTACACACTGTTCTACTGTTTGAATTTTTT 2326

AATATGAGCCCAAATTGTATAATCTTTTTTTTAATAAAGGGGAGAAAAATCAAAAAAAAAAAAAAAAAAGGGCGGCCGC 2403

Fig 20 (cont.)

```
TCCGGTCCANGAAAAAGCTGCTTGCACTAGGGGCATCCCGCCTGCCTGGTGAAAGGAACCGCAGCACACAGGGTGGGAG  79

GGCTTCCGATTTTAGCAGGGCGGCTTCCGGAAGGCGGAGCTCCAACCCCATTTCCTTTCTCTGGGCTGGTTCTGGCCCA 158

                                                          M   G   G   A   R        5
GCTGCACCTGCGTGTGGCCCTGGCTCCTCGGCTCCCTGCAGCTCCGAGGCAGCAGC ATG GGT GGC GCG CGG     229

 D   V   G   W   V   A   A   G   L   V   L   G   A   G   A   C   Y   C   I   Y   25
GAC GTG GGC TGG GTG GCA GCA GGG CTG GTC CTG GGC GCC GGC GCC TGC TAC TGT ATC TAC  289

 R   L   T   R   G   P   R   R   G   V   A   T   M   R   P   S   R   S   A   E   45
CGG CTG ACT CGG GGA CCG CGG CGA GGC GTC GCG ACC ATG CGC CCT TCG CGA TCC GCA GAA  349

 D   L   T   D   G   S   Y   D   D   I   L   N   A   E   Q   L   K   K   L   L   65
GAC CTA ACC GAT GGC TCC TAT GAC GAT ATC TTA AAT GCA GAG CAG CTT AAG AAA CTT CTG  409

 Y   L   L   E   S   T   D   D   P   V   I   T   E   K   A   L   V   T   L   G   85
TAT CTG CTG GAG TCA ACC GAC GAT CCT GTC ATT ACT GAA AAG GCC TTG GTC ACC TTG GGA  469

 N   N   A   A   F   S   T   N   Q   A   I   I   R   E   L   G   G   I   P   I   105
AAT AAT GCA GCC TTC TCC ACT AAC CAG GCC ATT ATT CGT GAG TTG GGT GGT ATC CCA ATT  529

 V   G   N   K   I   N   S   L   N   Q   S   I   K   E   K   A   L   N   A   L   125
GTT GGA AAC AAA ATC AAC TCC CTG AAC CAA AGT ATT AAA GAG AAA GCT TTA AAT GCA CTG  589

 N   N   L   S   V   N   V   E   N   Q   T   K   I   K   I   Y   V   P   Q   V   145
AAT AAC CTG AGT GTG AAT GTT GAA AAT CAA ACT AAG ATA AAG ATA TAC GTC CCT CAA GTC  649

 C   E   D   V   F   A   D                                                       152
TGT GAG GAC GTC TTT GCT GAC                                                      670
```

FIG. 21

```
                10                  20                  30                  40                  50
HUMAN   MALLSRPALT----LLLLLMAAVVRCQEQAQTTDWRATLKTIRNGVHKIDTYLNAALDLL
        : . .::: .    :::::. :..: :::.:::::::::::::::::.:::::::::::
MURINE  M-VTPRPAPARGPALLLLLLLATARGQEQDQTTDWRATLKTIRNGIHKIDTYLNAALDLL
                10         20         30         40         50

          60         70         80         90         100        110
        GGEDGLCQYKCSDGSKPFPRYGYKPSPPNGCGSPLFGVHLNIGIPSLTKCCNQHDRCYET
        :::::::::::::::::: :::::::::::::::::::::::::::::::::::::::::
        GGEDGLCQYKCSDGSKPVPRYGYKPSPPNGCGSPLFGVHLNIGIPSLTKCCNQHDRCYET
      60         70         80         90         100        110

          120        130        140        150        160        170
        CGKSKNDCDEEFQYCLSKICRDVQKTLGLTQHVQACETTVELLFDSVIHLGCKPYLDSQR
        :::::::::::::::::::::::::::::.:.:::::::::::::::::::::::::::
        CGKSKNDCDEEFQYCLSKICRDVQKTLGLSQNVQACETTVELLFDSVIHLGCKPYLDSQR
      120        130        140        150        160        170

          180        190
      : AACRCHYEEKTDL
        :::.:.::::::
        AACWCRYEEKTDL
      180        190
```

Fig. 12

```
                10        20        30        40        50        60
MURINE  MAQLGAVVAVASSFFCASLFSAVHKIEEGHIGVYYRGGALLTSTSGPGFHLMLPFITSYK
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
HUMAN   MAQLGAVVAVASSFFCASLFSAVHKIEEGHIGVYYRGGALLTSTSGPGFHLMLPFITSYK
                10        20        30        40        50        60

                70        80        90       100       110       120
        SVQTTLQTDEVKNVPCGTSGGVMIYFDRIEVVNFLVPNAVYDIVKNYTADYDKALIFNKI
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
        SVQTTLQTDEVKNVPCGTSGGVMIYFDRIEVVNFLVPNAVYDIVKNYTADYDKALIFNKI
                70        80        90       100       110       120

               130       140       150       160       170       180
        HHELNQFCSVHTLQEVYIELFDQIDENLKLALQQDLTSMAPGLVIQAVRVTKPNIPEAIR
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
        HHELNQFCSVHTLQEVYIELFDQIDENLKLALQQDLTSMAPGLVIQAVRVTKPNIPEAIR
               130       140       150       160       170       180

               190       200       210       220       230       240
        RNYELMESEKTKLLIAAQKQKVVEKEAETERKKALIEAEKVAQVAEITYGQKVMEKETEK
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
        RNYELMESEKTKLLIAAQKQKVVEKEAETERKKALIEAEKVAQVAEITYGQKVMEKETEK
               190       200       210       220       230       240
```

FIG. 23

```
                10        20        30        40        50        60
HUMAN   MNMTQARVLVAAVVGLVAVLLYASIHKIEEGHLAVYYRGGALLTSPSGPGYHIMLPFITT

MURINE  ------------------------------------------------------------

               70        80        90        100       110       120
        FRSVQTTLQTDEVKNVPCGTSGGVMIYIDRIEVVNMLAPYAVFDIVRNYTADYDKTLIFN
                        :::::::::::::::::::::::::::::::::::::::::::::
        ------------KNVPCGTSGGVMIYIDRIEVVNMLAPYAVFDIVRNYTADYDKTLIFN
                           10        20        30        40

               130       140       150       160       170       180
        KIHHELNQFCSAHTLQEVYIELFDQIDENLKQALQKDLNLMAPGLTIQAVRVTKPKIPEA
        :::::::::::::::::::::::::::::::::::::::: ::::::::::::::::::::
        KIHHELNQFCSAHTLQEVYIELFDQIDENLKQALQKDLNTMAPGLTIQAVRVTKPKIPEA
         50        60        70        80        90        100

               190       200       210       220       230       240
        IRRNFELMEAEKTKLLIAXQKQKVVEKEAETERKKAVIEAEKIAQVAKIRFQQKVMEKET
        ::::::::::::::::::.:::::::::::::::.:::::::::::::::::::::::::::
        IRRNFELMEAEKTKLLIAAQKQKVVEKEAETERKRAVIEAEKIAQVAKIRFQQKVMEKET
        110       120       130       140       150       160

               250       260       270       280       290       300
        EKRISEIEDAAFLAREKAKADAEYYAAHKYATSNKHKLTPEYLELKKYQAIASNSKIYFG
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
        EKRISEIEDAAFLAREKAKADAEYYAAHKYATSNKHKLTPEYLELKKYQAIASNSKIYFG
        170       180       190       200       210       220

               310       320       330       340
        SNIPNMFVDSSCALKYSDIRTGRESSLPSKEALEPSGENVIQNKESTG-
        :::.:::::::::::::: :::::.::. :: ::::::. :::::::.:
        SNIPSMFVDSSCALKYSDGRTGREDSLPPEEAREPSGESPIQNKENAGN
        230       240       250       260       270
```

FIG 24

```
                10        20        30        40        50        60
MURINE  MKLLCLVAVVGCLLVPPAQANKSSEDIRCKCICPPYRNISGHIYNQNVSQKDCNCLHVVE
        :::: :::::::::::::.:::::::::::::::::::::::::::::::::::::::::
HUMAN   MKLLSLVAVVGCLLVPPAEANKSSEDIRCKCICPPYRNISGHIYNQNVSQKDCNCLHVVE
                10        20        30        40        50        60

                70        80        90       100       110       120
        PMPVPGHDVEAYCLLCECRYEERSTTTIKVIIVIYLSVVGALLLYMAFLMLVDPLIRKPD
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
        PMPVPGHDVEAYCLLCECRYEERSTTTIKVIIVIYLSVVGALLLYMAFLMLVDPLIRKPD
                70        80        90       100       110       120

               130       140       150       160       170       180
        AYTEQLHNEEENEDARTMATAAASIGGPRANTVLERVEGAQQRWKLQVQEQRKTVFDRHK
        :::::::::::::::::.::.:::::.::::::::::::::::::::::::::::::::::
        AYTEQLHNEEENEDARSMAAAAASLGGPRANTVLERVEGAQQRWKLQVQEQRKTVFDRHK
               130       140       150       160       170       180

        MLS
        :::
        MLS
```

FIG 25

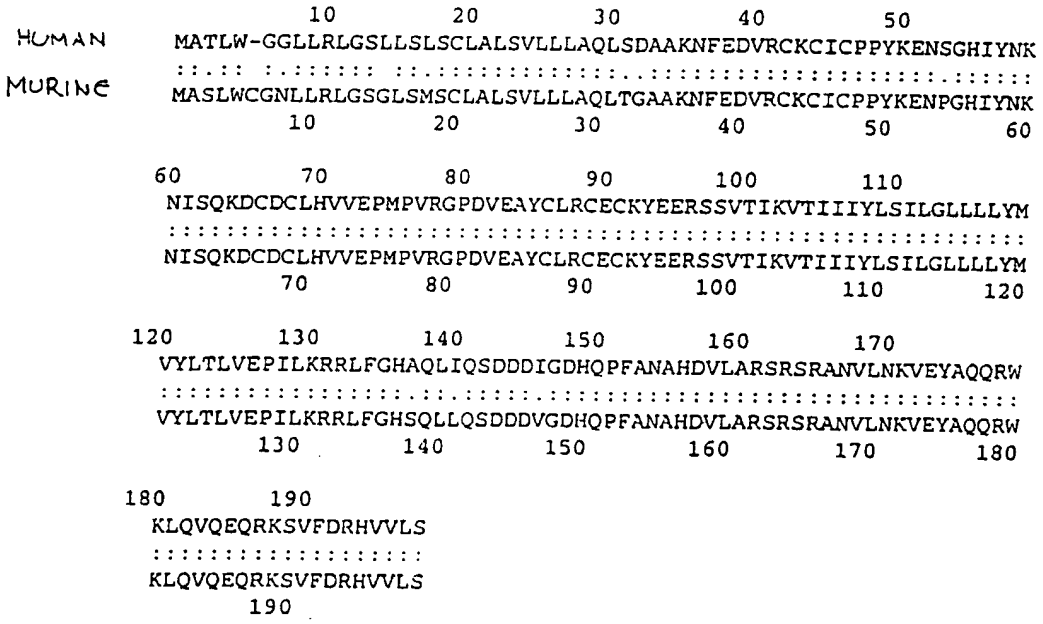

HUMAN
MURINE
MATLW-GGLLRLGSLLSLSCLALSVLLLAQLSDAAKNFEDVRCKCICPPYKENSGHIYNK
MASLWCGNLLRLGSGLSMSCLALSVLLLAQLTGAAKNFEDVRCKCICPPYKENPGHIYNK
NISQKDCDCLHVVEPMPVRGPDVEAYCLRCECKYEERSSVTIKVTIIIYLSILGLLLLYM
NISQKDCDCLHVVEPMPVRGPDVEAYCLRCECKYEERSSVTIKVTIIIYLSILGLLLLYM
VYLTLVEPILKRRLFGHAQLIQSDDDIGDHQPFANAHDVLARSRSRANVLNKVEYAQQRW
VYLTLVEPILKRRLFGHSQLLQSDDDVGDHQPFANAHDVLARSRSRANVLNKVEYAQQRW
KLQVQEQRKSVFDRHVVLS
KLQVQEQRKSVFDRHVVLS

FIG. 26

```
                10        20        30        40        50        60
HUMAN   MIRCGLACERCRWILPLLLLSAIAFDIIALAGRGWLQSSDHGQTSSLWWKCSQEGGGSGS
        :.:::::::::::::::::::::::::::::::::::.: ::::::::.: .:::::::
MURINE  MLRCGLACERCRWILPLLLLSAIAFDIIALAGRGWLQSSNHIQTSSLWWRCFDEGGGSGS
                10        20        30        40        50        60

                70        80        90       100       110       120
        YEEGCQSLMEYAWGRAAAAMLFCGFIILVICFILSFFALCGPQMLVFLRVIGGLLALAAV
        :..:::::::::::::::: :::::::: :::::::::::::::::::::::::::::.
        YDDGCQSLMEYAWGRAAAATLFCGFIILCICFILSFFALCGPQMLVFLRVIGGLLALAAI
                70        80        90       100       110       120

               130       140       150       160       170       180
        FQIISLVIYPVKYTQTFTLHANPAVTYIYNWAYGFGWAATIILIGCAFFFCCLPNYEDDL
        :::::::::::::::: ::.:::::.:::::::::::::::::::.:::::::::::::
        FQIISLVIYPVKYTQTFRLHDNPAVNYIYNWAYGFGWAATIILIGCSFFFCCLPNYEDDL
               130       140       150       160       170       180

               190
        LGNAKPRYFYTSAN
        ::.:::::::: .::
        LGAAKPRYFYPPAN
               190
```

FIG. 27

```
                10        20        30        40        50
MURINE    MAGIPGL-FILLVLLCVFMQVSPYTVPWKPTWPAYRLPVVLPQSTLNLAKADFDAKAKLE
          :::::::: :.:. :::.  :::::.:::::::::::::::::::::::::.:.: ::::
HUMAN     MAGIPGLLFLLFFLLCAVGQVSPYSAPWKPTWPAYRLPVVLPQSTLNLAKPDFGAEAKLE
                10        20        30        40        50        60

          60        70        80        90       100       110
           VSSSCGPQCHKGTPLPTYEEAKQYLSYETLYANGSRTETRVGIYILSNGEGRARGRDSEA
           :::::::::::::::::::::::::::::::::::::::::.::::::.. . :. ::: .
           VSSSCGPQCHKGTPLPTYEEAKQYLSYETLYANGSRTETQVGIYILSSSGDGAQHRDSGS
                   70        80        90       100       110       120

         120       130       140       150       160       170
           TGRSRRKRQIYGYDGRFSIFGKDFLLNYPFSTSVKLSTGCTGTLVAEKHVLTAAHCIHDG
           .:.:::::::::::.:::::::::::::::::::::::::::::::::::::::::::::
           SGKSRRKRQIYGYDSRFSIFGKDFLLNYPFSTSVKLSTGCTGTLVAEKHVLTAAHCIHDG
                  130       140       150       160       170       180

         180       190       200       210       220       230
           KTYVKGTQKLRVGFLKPKYKDGAEGDNSSSSAMPDKMKFQWIRVKRTHVPKGWIKGNAND
           :::::::::::::::::::::. :.:.:.::::.:::::::::::::::::::::::::::
           KTYVKGTQKLRVGFLKPKFKDGGRGANDSTSAMPEQMKFQWIRVKRTHVPKGWIKGNAND
                  190       200       210       220       230       240

         240       250       260       270       280       290
           IGMDYDYALLELKKPHKRQFMKIGVSPPAKQLPGGRIHFSGYDNDRPGNLVYRFCDVKDE
           ::::::::::::::::::.:::::::::::::::::::::::::::::::::::::::::
           IGMDYDYALLELKKPHKRKFMKIGVSPPAKQLPGGRIHFSGYDNDRPGNLVYRFCDVKDE
                  250       260       270       280       290       300

         300       310       320       330       340       350
           TYDLLYQQCDAQPGASGSGVYVRMWKRPQQKWERKIIGIFSGHQWVDMNGSPQDFNVAVR
           :::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
           TYDLLYQQCDAQPGASGSGVYVRMWKRQQQKWERKIIGIFSGHQWVDMNGSPQDFNVAVR
                  310       320       330       340       350       360

         360       370       380
           ITPLKYAQICYWIKGNYLDCREG
           :::::::::::::::::::::::
           ITPLKYAQICYWIKGNYLDCREG
                  370       380
```

FIG. 28

```
                10        20        30        40        50
HUMAN   MAPASR-----LLALWALAAVALPGSGAEGDGGWRPGGPG---AVAEEERCTVERRADLT
        ::.:.:      :..:: ...: ::.:   :.:::::: :   :: ::::::::::::.:
MURINE  MAAAGRRGLLLLFVLWMMVTVILPAS---GEGGWKQNGLGIAAAVMEEERCTVERRAHIT
           10        20        30        40        50

        60        70        80        90        100       110
YAEFVQQYAFVRPVILQGLTDNSRFRALCSRDRLLASFGDRVVRLSTANTYSYHKVDLPF
:.:.:.:::.:::::::::::::::::::. ::::::: .:::::::::::::.::::::
YSEFMQHYAFLKPVILQGLTDNSKFRALCSRENLLASFGDNIVRLSTANTYSYQKVDLPF
 60        70        80        90        100       110

      120       130       140       150       160       170
QEYVEQLLHPQDPTSLGNDTLYFFGDNNFTEWASLFRHYSPPPFGLLGTAPAYSFGIAGA
:::::::.:::::.:::::::::::::::::::::.:::::: :::::.::::::::::
QEYVEQLLQPQDPASLGNDTLYFFGDNNFTEWASLFQHYSPPPFRLLGTTPAYSFGIAGA
120       130       140       150       160       170

      180       190       200       210       220       230
GSGVPFHWHGPGYSEVIYGRKRWFLYPPEKTPEFHPNKTTLAWLRDTYPALPPSARPLEC
::::::::::::.:::::::::::::::::::::::::::::::: ..:::.:. :::::::
GSGVPFHWHGPGFSEVIYGRKRWFLYPPEKTPEFHPNKTTLAWLLEIYPSLALSARPLEC
180       190       200       210       220       230

      240       250       260
TIRAGEVLYFPDRWWHATLNLDTSVFISTFLG
::.:::::::::::::::::::::::::::::
TIQAGEVLYFPDRWWHATLNLDTSVFISTFLG
240       250       260
```

FIG. 29

```
                10        20        30        40        50        60
HUMAN   MDNRFATAFVIACVLSLISTIYMAASIGTDFWYEYRSPVQENSSDLNKSIWDEFISDEAD
        :::::::::::::::::::::::::::::::::::::::::.:::::: :: :..:.:::::
MURINE  MDNRFATAFVIACVLSLISTIYMAASIGTDFWYEYRSPIQENSSDSNKIAWEDFLGDEAD
                10        20        30        40        50        60

                70        80        90        100       110       120
        EKTYNDALFRYNGTVGLWRRCITIPKNMHWYSPPERTESFDVVTKCVSFTLTEQFMEKFV
        ::::::.:::::::..:::::::::::: :::.:::::::::::::::::.::::::.:
        EKTYNDVLFRYNGSLGLWRRCITIPKNTHWYAPPERTESFDVVTKCMSFTLNEQFMEKYV
                70        80        90        100       110       120

               130       140       150       160       170       180
        DPGNHNSGIDLLRTYLWRCQFLLPFVSLGLMCFGALIGLCACICRSLYPTIATGILHLLA
        :::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
        DPGNHNSGIDLLRTYLWRCQFLLPFVSLGLMCFGALIGLCACICRSLYPTLATGILHLLA
               130       140       150       160       170       180

               190       200       210       220       230       240
        GLCTLGSVSCYVAGIELLHQKLELPDNVSGEFGWSFCLACVSAPLQFMASALFIWAAHTN
        :::::::::::::::::::::.::: .:::::::::::::::::::::::::.::::::::
        GLCTLGSVSCYVAGIELLHQKVELPKDVSGEFGWSFCLACVSAPLQFMAAALFIWAAHTN
               190       200       210       220       230       240

               250
        RKEYTLMKAYRVA
        :::::::::::::
        RKEYTLMKAYRVA
               250
```

FIG. 30

```
                10         20         30         40         50
MURINE    MGGARDVGWVAAGLVLGAGACYCIYRLTRGPRRGVATM--RPSRSAEDLTDGSYDDILNA
          :::.:.:::::::::::::::::::::::::::: ::::    .  :::.:::::::::::::::
HUMAN     MGGPRGAGWVAAGLLLGAGACYCIYRLTRGRRRGDRELGIRSSKSAEDLTDGSYDDVLNA
                10         20         30         40         50         60

          60         70         80         90         100        110
          EQLKKLLYLLESTDDPVITEKALVTLGNNAAFSTNQAIIRELGGIPIVGNKINSLNQSIK
          :::.:::::::::::.:::.:::.:::::::::::::::::::.:::::::::::  :::::
          EQLQKLLYLLESTEDPVIIERALITLGNNAAFSVNQAIIRELGGIPIVANKINHSNQSIK
                  70         80         90         100        110        120

          120        130        140        150
          EKALNALNNLSVNVENQTKIKIYVPQVCEDVFA----------------------------
          :::::::::::::::::::::::::::::::.
          EKALNALNNLSVNVENQIKIKIYISQVCEDVFSGPLNSAVQLAGLTLLTNMTVTNDHQHM
                 130        140        150        160        170        180


          ------------------------------------------------------------

          LHSYITDLFQVVLTGNGNTKVQXLKLLLNLAENPAMTEGLLRAQVDSSFLFLYDXHVAXE
                 190        200        210        220        230        240


          ---------D
                   .
          XLLQYLRFSE
                 250
```

FIG. 31

```
humutntalign
ALIGN calculates a global alignment of two sequences
version 2.0uPlease cite: Myers and Miller, CABIOS (1989)
> mut180                                          1570 aa vs. > hut180
                          1203 aa scoring matrix: pam120.mat, gap penalties: -12/-4
55.0% identity;          Global alignment score: 2219

10           20         30             40         50
GTCGACCCACGCGTCCG---GGCCGGGGTCCTGA-----GCCGGAGCCGGAGCGCGCGCC
:::::::::::::::::   ::  . :::. ::::.     :::... ::::.:: ::::::
GTCGACCCACGCGTCCGCGTGGATATGGAGCTGGCTGCTGCCAAGTCCGGGGCCCGCGCC
10         20         30         40         50         60

60                            70         80         90
GCTGCCCAGC----CC------CGC--------CGCGCCG-GCCCCGCAGAT-GGTGACT
:::::: :::    ::       : :        ::::::  :: :::::: : :: :::
GCTGCCTAGCGCGTCCTGGGGACTCTGTGGGGACGCGCCCCGCGCCGCGGCTCGGGGACC
70         80         90        100        110        120

100            110         120          130
C-----------CGCGGCCCGC---GCCC-GCCCGGG-GCCCCGCGCTC---CTCCTCCT
:            ::: :: :::   :::: :: :  : ::::::::::   ::::: ::
CGTAGAGCCCGGCGCTGCGCGCATGGCCCTGCTCTCGCGCCCCGCGCTCACCCTCCTGCT
130        140        150        160        170        180

140        150           160        170        180        190
CCTGCTGCTGGCCACTGCGCGCGGG---CAGGAACAGGACCAGACCACCGACTGGAGGGC
::: ::  ::::::.:::    :.::   ::::::.:::: ::::::::::::::::::.::
CCTCCTCATGGCCGCTGTTGTCAGGTGCCAGGAGCAGGCCCAGACCACCGACTGGAGAGC
190        200        210        220        230        240

200        210        220        230        240        250
CACCCTCAAGACCATCCGCAACGGCATCCACAAGATAGACACGTACCTCAACGCCGCGCT
:::::: :::::::::::: :::::::.: :: ::::::::::::::::: ::::::::  :
CACCCTGAAGACCATCCGGAACGGCGTTCATAAGATAGACACGTACCTGAACGCCGCCTT
250        260        270        280        290        300

260        270        280        290        300        310
GGACCTGCTGGGCGGGGAGGACGGGCTCTGCCAGTACAAGTGCAGCGACGGATCGAAGCC
:::::: ::::: :: :::::::: :::::::::: ::.::::: :::::::: :::::
GGACCTCCTGGGAGGCGAGGACGGTCTCTGCCAGTATAAATGCAGTGACGGATCTAAGCC
310        320        330        340        350        360

320        330        340        350        360        370
TGTTCCACGCTATGGATATAAACCATCTCCACCAAATGGCTGTGGCTCTCCACTGTTTGG
: : ::::: :::::.:::::::: :: :::::.::::: ::::::::::::::::::::
TTTCCCACGTTATGGTTATAAACCCTCCCCACCGAATGGATGTGGCTCTCCACTGTTTGG
370        380        390        400        410        420

380        390        400        410        420        430
CGTTCATCTGAACATAGGTATCCCTTCCCTGACCAAGTGCTGCAACCAGCACGACAGATG
 :::::::: :::::.:::::::::::::::::::: ::::: ::::::::.:::::::.::
TGTTCATCTTAACATTGGTATCCCTTCCCTGACAAAGTGTTGCAACCAACACGACAGGTG
430        440        450        460        470        480

440        450        460        470        480        490
CTATGAGACCTGCGGGAAAAGCAAGAACGACTGTGACGAGGAGTTCCAGTACTGCCTCTC
:::::::::::: :: :::::::::: :::::::: ::.::.::::::: ::::::::
CTATGAGACCTGTGGCAAAAGCAAGAATGACTGTGATGAAGAATTCCAGTATTGCCTCTC
490        500        510        520        530        540
```

FIG. 32 (10F3)

```
500        510        520        530        540        550
CAAGATCTGCAGAGACGTGCAGAAGACGCTCGGACTATCTCAGAACGTCCAGGCATGTGA
:::::::::: :::: ::.:::::.::.:: :::::::.::::: : :: ::::::::::
CAAGATCTGCCGAGATGTACAGAAAACACTAGGACTAACTCAGCATGTTCAGGCATGTGA
550        560        570        580        590        600

560        570        580        590        600        610
GACAACGGTGGAGCTCCTCTTTGACAGCGTCATCCATTTAGGCTGCAAGCCATACCTGGA
.::::::.:::::::::: : :::::::: :: :: :::::::: :: ::.::::: :::::
AACAACAGTGGAGCTCTTGTTTGACAGTGTTATACATTTAGGTTGTAAACCATATCTGGA
610        620        630        640        650        660

620        630        640        650        660
CAGCCAGCGGGCTGCATGCTGGTGTCGTTATGAAGAAAAAAACAGATCTATAAAG---ACC
:::::::.::.:: :::::::.::::::.:::::::::::::::::.::::::.::::    :
CAGCCAACGAGCCGCATGCAGGTGTCATTATGAAGAAAAAAACTGATCTTTAAAGGAGATG
670        680        690        700        710        720

670        680        690        700         710        720
CTGACTGCTGGAGAGCAGGCGAGAATGGAGGATCAT-CCTT-GCCAAAGATCGGATGCTT
: :::.::::.:.:: :::. ::..:::::::.::.::: :::: : :::: :.: .::: ::
CCGACAGCTAGTGA-CAGATGAAGATGGAAGAACATACCTTTGACAAATAACTAATGTTT
730        740        750        760        770

730        740        750        760        770        780
TAACAGCCTAATGTTGCCTTAGTTTTGTGTCGATGGGTCATTTTGAGACCTTTCTATACT
:.::::.: ::::.. :: :::: :::::::  .:.::.: ::::::::::::. .:::
TTACAACATAAAACTGTCTTATTTTTGTG--AAAGGATTATTTTGAGACCTTAAAATA--
780        790        800         810        820        830

790        800        810        820        830        840
GTGTCTTTTTTTAGAACCTCAAAGTGAAAACGGTGGGGGGCCAGGCAGAAACAGAGGGAG
     .:::.:..    :: .:.:: :::::          : :.:::.::: ::.:.:.:
-----ATTTATAT----CTTGATGTTAAAACCT-------CAAAGCAAAAAAAGTGAGGG
840            850               860        870

850        860        870        880        890        900
AGCATGCTTGGGATGGGGAGCGAGCAGGACATCCAAGAGCATGCCTTCCTGAGACTCGCT
:: ..:       ::.::.: :.:::   :        ::.:: ::::
AGATAG-------TGAGGGGAGGGCA---C--------GCTTGTCTTC------------
880               890                  900

910        920        930        940        950        960
GTCTTGGTGGCTCCCCCAAACTGGGAAGAAAAGCTTAAGCTCGTGTGACTTGGTGTTCAT
::. :::. :: :::::               ::.:. ::::      :::.     :.:
-TCA-GGTATCTTCCCCA-------------GCATT-GCTC-----CCTTA-----CTT
910         920                    930                   940

970        980        990       1000       1010       1020
AGTTGTACTTAACAATAAAAATGAAAGCAAATGTAAAATTCATTGTAAGGACTTTTCAGC
:::. :.:                    :::::::                   :::
AGTA-TGC-----------------CAAATGT----------------CTT------
950

1030       1040       1050       1060       1070       1080
ATTATTTTATTTTGAAATACAGGCCAATCTTCCCTTAGAACTATTATTTATTTTGAAATT
                     :.:::::.:::   .:.::::.: :. ::.:::.:
--------------------GACCAAT-ATC---AAAAACAAGTGCTTGTTTAG-----
960          970        980
```

FIG 32 (2 OF 3)

```
 1090       1100       1110       1120       1130       1140
 TCAGATGTACATTTATACCTGGAAAAACTATTAATTCTCCATTTTTATTATACATAATGT
  :.:: :.: .:: :.:  .:::::.:      ::...::: :::::
 -CGGA-GAATTTTGAAAAGAGGAATA-----TATAACTCAATTTT--------------
 990        1000       1010            1020

 1150       1160       1170       1180       1190       1200
 GTTGTTTCTCTGAAGCCCACTAAGATAGGTATAAATATGTTACTCAAAACTACACGGTTT
                    :::                                :::  :::. ::.
 -----------------CAC--------------------------AAC--CACATTTA
 1030                                  1040

 1210       1220       1230       1240       1250       1260
 CCAAATGTGCATCTCTTGTACAGTTGGAATCACGGTTGGTACTTCTCTGGAGAGACGCCC
 :::::                 :...:..:::: . .:...: :
 CCAAA----------------AAAAGAGATCAAATATAAAATT----------------
 1050       1060

 1270       1280       1290       1300       1310       1320
 CAGGACATCTGAGTGTTGGGATGTGCACAGAATTCAGAAGCCCAGCTTCCTGTCTCACAA
      :::::. :.:::                    :.:..   ::.:.:  :.:::
 -----CATCATAATGT-----------------CTGTT---CAACAT--TATCT-----
 1070                          1080          1090

 1330       1340       1350       1360       1370       1380
 ACCGCTTAGAGTGAATGTCCTTCCTCTCCTGCTGTGAGCTCTAGGAATGACGGGTTTAAC
           :...::                              ...:::::. :...:::.:
 -----------TATTTG-------------------------GAAAATGGGGAAATTATC
 1100                                1110

 1390       1400       1410       1420       1430       1440
 GGGCCAAGCCGAGCTCTGAATCAGTGCGCTATCTGCTGCTGAGGTTGTGGTTACTCCCTC
 .                             ::.::.       :: .: :: :::::
 A--------------------------CTTACA-------AGTATTTGTTTACT-----
 1120                                      1130       1140

 1450       1460       1470       1480       1490       1500
 ATCCCCGTTTTCCATCTTCTATCCTGGAGTAGTGTTAAAAGTCTGACATTTTCTAATGGA
                          .:.:.: ::.::: .:  ::::::
 -------------------------ATGAAAT-TTTAAATAC--ACATTT---------
 1150        1160

 1510       1520       1530       1540       1550       1560
 GGTCTTAATAAAAGCTATTTACTTCTTGGTAAAAAAAAAAAAAAAAAAAAAAAAAAAGGGC
           :.::          :::.      :::::::::::::::::::::::::::
 -----------ATGC---------CTAG-----AAAAAAAAAAAAAAAAAAAAAAAAGGGC
 1170            1180       1190

 1570
 GGCCG-
 :::::
 GGCCGC
 1200
```

FIG 32 (3 of 3)

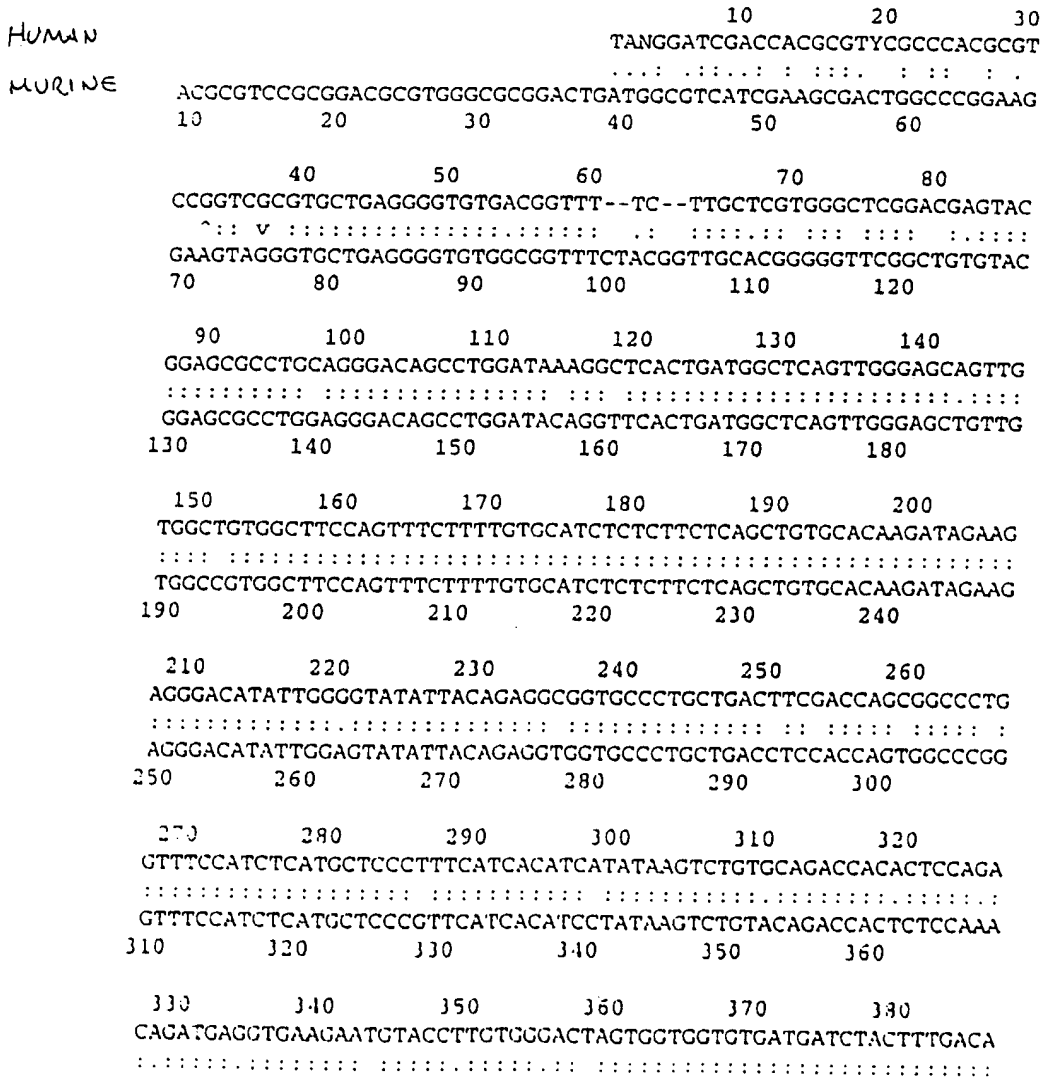

HUMAN
MURINE
10 20 30
TANGGATCGACCACGCGTYCGCCCACGCGT
ACGCGTCCGCGGACGCGTGGGCGCGGACTGATGGCGTCATCGAAGCGACTGGCCCGGAAG
10 20 30 40 50 60
40 50 60 70 80
CCGGTCGCGTGCTGAGGGGTGTGACGGTTT--TC--TTGCTCGTGGGCTCGGACGAGTAC
GAAGTAGGGTGCTGAGGGGTGTGGCGGTTTCTACGGTTGCACGGGGGTTCGGCTGTGTAC
70 80 90 100 110 120
90 100 110 120 130 140
GGAGCGCCTGCAGGGACAGCCTGGATAAAGGCTCACTGATGGCTCAGTTGGGAGCAGTTG
GGAGCGCCTGGAGGGACAGCCTGGATACAGGTTCACTGATGGCTCAGTTGGGAGCTGTTG
130 140 150 160 170 180
150 160 170 180 190 200
TGGCTGTGGCTTCCAGTTTCTTTTGTGCATCTCTCTTCTCAGCTGTGCACAAGATAGAAG
TGGCCGTGGCTTCCAGTTTCTTTTGTGCATCTCTCTTCTCAGCTGTGCACAAGATAGAAG
190 200 210 220 230 240
210 220 230 240 250 260
AGGGACATATTGGGGTATATTACAGAGGCGGTGCCCTGCTGACTTCGACCAGCGGCCCTG
AGGGACATATTGGAGTATATTACAGAGGTGGTGCCCTGCTGACCTCCACCAGTGGCCCGG
250 260 270 280 290 300
270 280 290 300 310 320
GTTTCCATCTCATGCTCCCTTTCATCACATCATATAAGTCTGTGCAGACCACACTCCAGA
GTTTCCATCTCATGCTCCCGTTCATCACATCCTATAAGTCTGTACAGACCACTCTCCAAA
310 320 330 340 350 360
330 340 350 360 370 380
CAGATGAGGTGAAGAATGTACCTTGTGGGACTAGTGGTGGTGTGATGATCTACTTTGACA

FIG 33 (1 OF 4)

```
 CTGATGAAGTGAAGAACGTACCATGTGGAACCAGTGGTGGTGTGATGATCTACTTTGACA
370        380        390        400        410        420

 390        400        410        420        430        440
GAATTGAAGTGGTGAACTTCCTGGTCCCGAACGCAGTGTATGATATAGTGAAGAACTATA
::::::::::::::::::::::::::::::.:: ::::::::::::::::::::::::::::
GAATTGAAGTGGTGAACTTCCTGGTCCCAAATGCAGTGTATGATATAGTGAAGAACTATA
430        440        450        460        470        480

 450        460        470        480        490        500
CTGCTGACTATGACAAGGCCCTCATCTTCAACAAGATCCACCACGAACTGAACCAGTTCT
::::.:::::::::::::::::::::::::::::::::::: :: ::.:: ::::::::::
CTGCAGACTATGACAAGGCCCTCATCTTCAACAAGATCCATCATGAGCTTAACCAGTTCT
490        500        510        520        530        540

 510        520        530        540        550        560
GCAGTGTGCACACGCTTCAAGAGGTCTACATTGAGCTGTTTGATCAGATTGATGAAAATC
:::: :: :: :: ::::::.::.::::: :: ::::::::::::::::::::::::::: :
GCAGCGTTCATACTCTTCAGGAAGTCTATATCGAGCTGTTTGATCAAATTGATGAAAACC
550        560        570        580        590        600

 570        580        590        600        610        620
TCAAACTGGCTTTGCAACAGGACCTGACCTCCATGGCCCCTGGGCTGGTCATTCAAGCTG
::::. ::::::::::.::::::::::: :::::::::::::::::::: :: :::::::
TCAAGTTGGCTTTGCAGCAGGACCTGACTTCCATGGCCCCTGGGCTGGTTATCCAAGCTG
610        620        630        640        650        660

 630        640        650        660        670        680
TGCGGGTAACAAAGCCCAACATACCAGAGGCAATCCGCAGAAACTACGAGTTGATGGAAA
:::::.::.::::::::::: :::::.:::::::::::::::::::: ::: ::::::::::
TGCGAGTGACAAAGCCCAATATACCTGAGGCAATCCGCAGGAACTATGAGCTGATGGAAA
670        680        690        700        710        720

 690        700        710        720        730        740
GTGAGAAGACAAAGCTTCTCATTGCCGCCCAGAAACAGAAGGTGGTGGAAAAGGAAGCAG
: ::::::::::.::::::::::::::: :::::::::.:::::::::::::::::::.::::
GCGAGAAGACGAAGCTTCTCATTGCAGCCCAGAAGCAGAAGGTGGTGGAAAAGGAGGCAG
730        740        750        760        770        780

 750        760        770        780        790        800
AGACAGAGCCGAAGAAGGCGCTCATTGAGGCAGAAAAAGTGGCCCAGGTGGCTGAGATCA
:.::::::: :::::::::: :::::::::::::::::::::::: ::::: ::.::.::::
AAACAGAGAGGAAGAAGGCCCTCATTGAGGCAGAAAAAGTGGCACAGGTTGCAGAAATCA
790        800        810        820        830        840

 810        820        830        840        850        860
CCTACGGGCAGAAGGTGATGGAGAAGGAGACTGAGAAGAAGATTTCAGAAATTGAAGATG
:::: :::::.:::::::::::::::::::::::::::::: .: . :..:. ::.:: :
CCTATGGGCAAAAGGTGATGGAGAAGGAGACAGAGAAGAATGTGAAAAGATGTGTAG-TC
850        860        870        880        890        900

 870        880        890        900        910        920
CTGCATTT-CTGGCCCCGGGAGAAGGCAAAGGCAGATGCTGAGTGCTACACTG--CTATGA
::: .::. :.:      :. .:..:: .:::::  .  ::  . ::.::::     :: ::.
CTGAGTTAACAGTT--TGACAAGAGCCTAAGCATGGCCTTCAGGCAACACGTACCTCTGG
910        920        930        940        950        960
```

FIG 33 (2 OF 4)

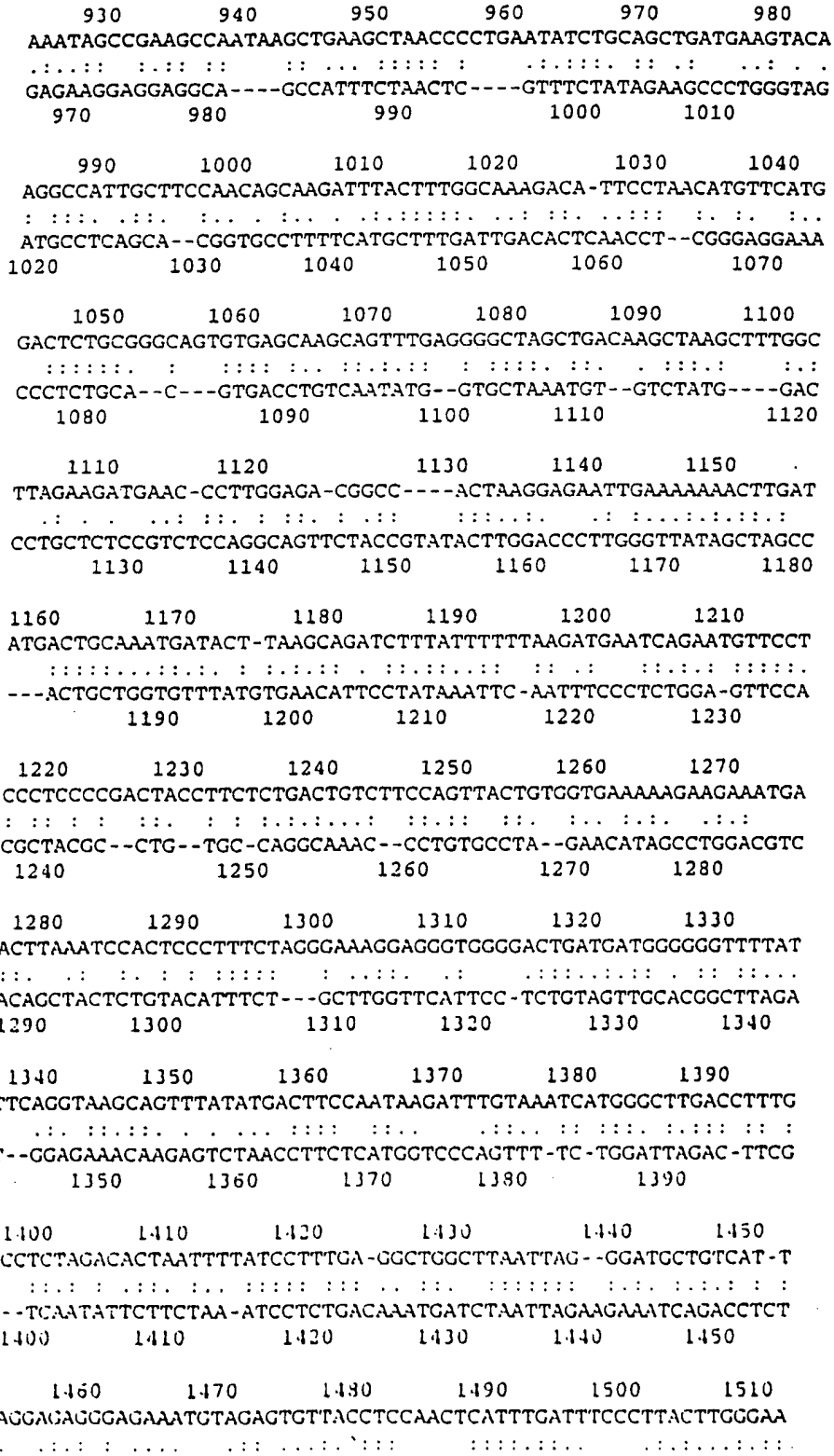

930 940 950 960 970 980
AAATAGCCGAAGCCAATAAGCTGAAGCTAACCCCTGAATATCTGCAGCTGATGAAGTACA
GAGAAGGAGGAGGCA----GCCATTTCTAACTC----GTTTCTATAGAAGCCCTGGGTAG
970 980 990 1000 1010
990 1000 1010 1020 1030 1040
AGGCCATTGCTTCCAACAGCAAGATTTACTTTGGCAAAGACA-TTCCTAACATGTTCATG
ATGCCTCAGCA--CGGTGCCTTTTCATGCTTTGATTGACACTCAACCT--CGGGAGGAAA
1020 1030 1040 1050 1060 1070
1050 1060 1070 1080 1090 1100
GACTCTGCGGGCAGTGTGAGCAAGCAGTTTGAGGGGCTAGCTGACAAGCTAAGCTTTGGC
CCCTCTGCA--C---GTGACCTGTCAATATG--GTGCTAAATGT--GTCTATG----GAC
1080 1090 1100 1110 1120
1110 1120 1130 1140 1150
TTAGAAGATGAAC-CCTTGGAGA-CGGCC----ACTAAGGAGAATTGAAAAAAACTTGAT
CCTGCTCTCCGTCTCCAGGCAGTTCTACCGTATACTTGGACCCTTGGGTTATAGCTAGCC
1130 1140 1150 1160 1170 1180
1160 1170 1180 1190 1200 1210
ATGACTGCAAATGATACT-TAAGCAGATCTTTATTTTTTAAGATGAATCAGAATGTTCCT
---ACTGCTGGTGTTTATGTGAACATTCCTATAAATTC-AATTTCCCTCTGGA-GTTCCA
1190 1200 1210 1220 1230
1220 1230 1240 1250 1260 1270
CCCTCCCCGACTACCTTCTCTGACTGTCTTCCAGTTACTGTGGTGAAAAAGAAGAAATGA
CGCTACGC--CTG--TGC-CAGGCAAAC--CCTGTGCCTA--GAACATAGCCTGGACGTC
1240 1250 1260 1270 1280
1280 1290 1300 1310 1320 1330
ACTTAAATCCACTCCCTTTCTAGGGAAAGGAGGGTGGGGACTGATGATGGGGGGTTTTAT
ACAGCTACTCTGTACATTTCT---GCTTGGTTCATTCC-TCTGTAGTTGCACGGCTTAGA
1290 1300 1310 1320 1330 1340
1340 1350 1360 1370 1380 1390
TTCAGGTAAGCAGTTTATATGACTTCCAATAAGATTTGTAAATCATGGGCTTGACCTTTG
T--GGAGAAACAAGAGTCTAACCTTCTCATGGTCCCAGTTT-TC-TGGATTAGAC-TTCG
1350 1360 1370 1380 1390
1400 1410 1420 1430 1440 1450
ACCTCTAGACACTAATTTTATCCTTTGA-GGCTGGCTTAATTAG--GGATGCTGTCAT-T
A--TCAATATTCTTCTAA-ATCCTCTGACAAATGATCTAATTAGAAGAAATCAGACCTCT
1400 1410 1420 1430 1440 1450
1460 1470 1480 1490 1500 1510
AAGGAGAGGGAGAAATGTAGAGTGTTACCTCCAACTCATTTGATTTCCCTTACTTGGGAA

FIG 33 (3 of 4)

```
    TTCCTGTGTGCATTGCTGGGACAAATGCCTC-----CATTAGAAA----ATTCAAAGAAA
      1460       1470       1480            1490           1500

          1520       1530         1540       1550       1560
    AATGCAGTCCAGTGTTCTCACCTCTG--CCTCCAAGGTAGGAGATGTCTGTGGGTGAGGC
    .. . :.:: ::..: v::.     ::  :::: :::: .::.  ::: : : ..::. :
    GTCATAATCGAGAAT-CTCTTTGGTGGTCCTCTAAGGCGGGT--TGTTTTTCAATGTTGT
     1510       1520        1530       1540          1550       1560

 1570       1580       1590       1600       1610       1620
    TYWKCAACTGAGCAAATATGTGCCTGTGAGTTTGCCAGTAGAGCTGTGAAGAAACAGCTG
    :   :..  ::::... : :::  . : :.: :     ::.:. : : :.:::: .  :.
    TG-TCTT-GGAGCTTGGAGGTGAAATTCAATGT----TTAAAATTTTTAGGAAATTTATA
          1570       1580       1590           1600       1610

 1630       1640       1650       1660       1670       1680
    CAGAGAA-CATTTGACCTTCCTGGCATTCTTGTCTGCATGTGTGTGAGTTATTTTAGAGG
    ::.:::: :.::::.:  ..  :.  .:  .:::   ::::.....:...:....:.:::
    CAAAGAAACTTTTAAATAAAGTATATTGAATGT-GCCATGAAAAAAAAAAAAAAAAAAGG
    1620       1630       1640       1650       1660       1670

 1690       1700       1710       1720       1730       1740
    TGTGCTTTCTTGAGCCCTCATAAGGAAGTACTGGTGCTAGGTTTTGCAAGATTTKGTATA
       ::
    GCGGCCG
     1680
```

FIG 33 (4 OF 4)

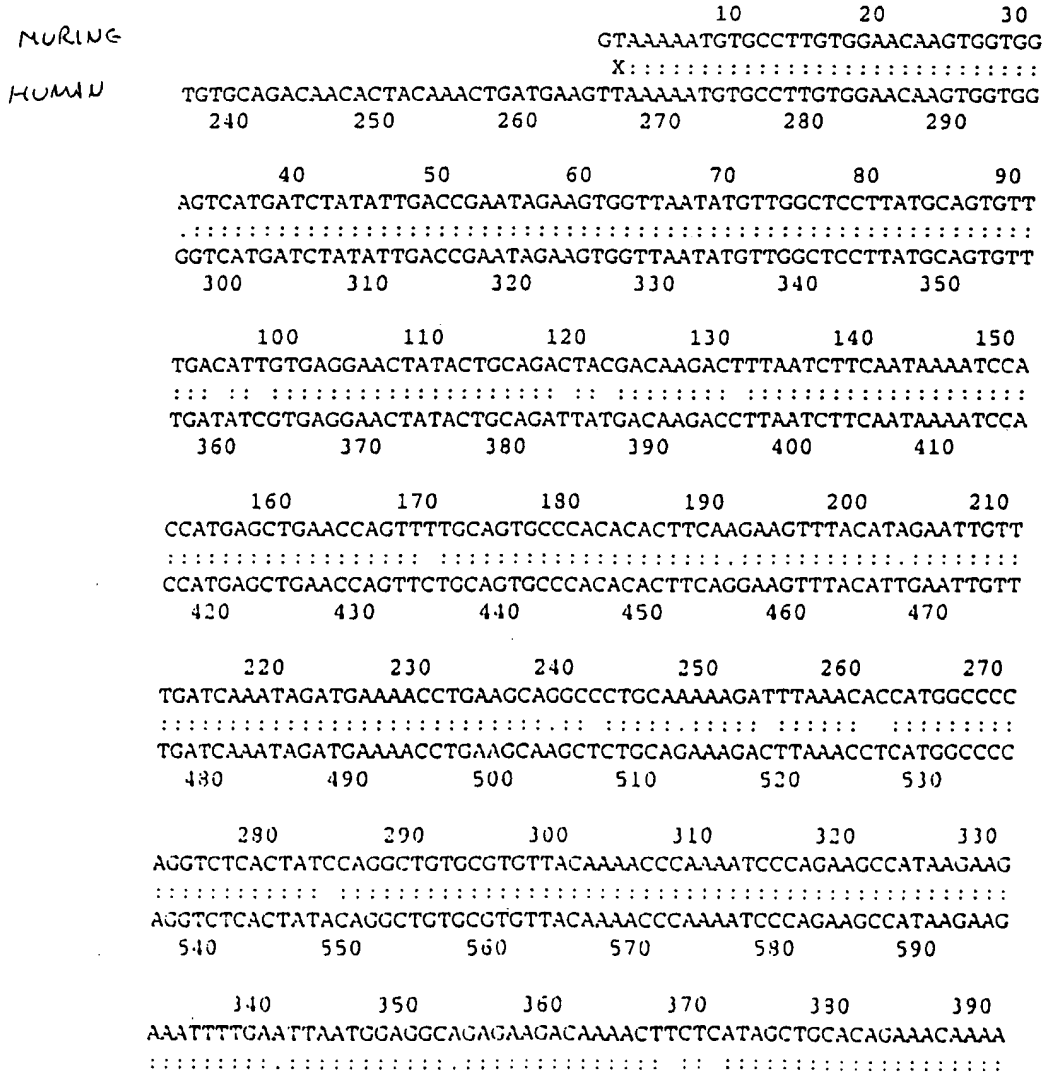

MURINE
HUMAN
10 20 30
GTAAAAATGTGCCTTGTGGAACAAGTGGTGG
X
TGTGCAGACAACACTACAAACTGATGAAGTTAAAAATGTGCCTTGTGGAACAAGTGGTGG
240 250 260 270 280 290
40 50 60 70 80 90
AGTCATGATCTATATTGACCGAATAGAAGTGGTTAATATGTTGGCTCCTTATGCAGTGTT
GGTCATGATCTATATTGACCGAATAGAAGTGGTTAATATGTTGGCTCCTTATGCAGTGTT
300 310 320 330 340 350
100 110 120 130 140 150
TGACATTGTGAGGAACTATACTGCAGACTACGACAAGACTTTAATCTTCAATAAAATCCA
TGATATCGTGAGGAACTATACTGCAGATTATGACAAGACCTTAATCTTCAATAAAATCCA
360 370 380 390 400 410
160 170 180 190 200 210
CCATGAGCTGAACCAGTTTTGCAGTGCCCACACACTTCAAGAAGTTTACATAGAATTGTT
CCATGAGCTGAACCAGTTCTGCAGTGCCCACACACTTCAGGAAGTTTACATTGAATTGTT
420 430 440 450 460 470
220 230 240 250 260 270
TGATCAAATAGATGAAAACCTGAAGCAGGCCCTGCAAAAAGATTTAAACACCATGGCCCC
TGATCAAATAGATGAAAACCTGAAGCAAGCTCTGCAGAAAGACTTAAACCTCATGGCCCC
480 490 500 510 520 530
280 290 300 310 320 330
AGGTCTCACTATCCAGGCTGTGCGTGTTACAAAACCCAAAATCCCAGAAGCCATAAGAAG
AGGTCTCACTATACAGGCTGTGCGTGTTACAAAACCCAAAATCCCAGAAGCCATAAGAAG
540 550 560 570 580 590
340 350 360 370 330 390
AAATTTTGAATTAATGGAGGCAGAGAAGACAAAACTTCTCATAGCTGCACAGAAACAAAA

FIG 34 (10F6)

```
AAATTTTGAGTTAATGGAGGCTGAGAAGACAAAACTCCTTATAGCTGCACAGAAACAAAA
  600       610       620       630       640       650

      400       410       420       430       440       450
GGTGGTGGAGAAAGAAGCTGAGACGGAGAGGAAAAGGGCTGTTATAGAAGCAGAGAAGAT
::: :::::.:::::::::::::::::::::::::.:::.:::::::::::::::::::::
GGTTGTGGAAAAAGAAGCTGAGACAGAGAGGAAAAAGGCAGTTATAGAAGCAGAGAAGAT
  660       670       680       690       700       710

      460       470       480       490       500       510
TGCACAAGTAGCAAAAATTCGATTTCAACAGAAAGTGATGGAGAAAGAAACTGAAAAACG
:::::::::.:::::::::::.:::::.:::::::::::::::::::::::::::::.::
TGCACAAGTGGCAAAAATTCGGTTTCAGCAGAAAGTGATGGAAAAAGAAACTGAAAAGCG
  720       730       740       750       760       770

      520       530       540       550       560       570
CATTTCTGAGATTGAAGATGCTGCGTTCCTGGCCCGAGAGAAGGCAAAAGCAGATGCCGA
::::::::::.:: :::::::::::.:::::::::::::::::::.::.::::::::::: ::
CATTTCTGAAATCGAAGATGCTGCATTCCTGGCCCGAGAGAAAGCGAAAGCAGATGCTGA
  780       790       800       810       820       830

      580       590       600       610       620       630
GTATTACGCTGCACACAAATACGCCACCTCAAACAAGCACAAACTGACCCCAGAGTATCT
.:::::: :::::::::::::: :::::::::::::::::::. ::::::::.::.::::::
ATATTATGCTGCACACAAATATGCCACCTCAAACAAGCACAAGTTGACCCCGGAATATCT
  840       850       860       870       880       890

      640       650       660       670       680       690
GGAGCTCAAGAAATACCAGGCCATTGCCTCAAACAGTAAGATCTACTTTGGCAGCAACAT
::::::::::.:::::::::::::::::: ::.:::::::::::::::: ::::::::::::::
GGAGCTCAAAAAGTACCAGGCCATTGCTTCTAACAGTAAGATCTATTTTGGCAGCAACAT
  900       910       920       930       940       950

      700       710       720       730       740       750
CCCCAGCATGTTTGTGGACTCCTCCTGTGCTCTGAAATACTCTGATGGTAGGACTGGGAG
::: :.::::::: :::::::::::: :::::: ::::::: ::.:::. ::::::::::.::
CCCTAACATGTTCGTGGACTCCTCATGTGCTTTGAAATATTCAGATATTAGGACTGGAAG
  960       970       980       990      1000      1010

      760       770       780       790       800       810
AGAAGACTCCCTTCCCCCAGAGGAGGCCCGTGAGCCCTCTGGAGAGAGCCCCATCCAAAA
:::::.:::: :: ::: :..:::::::: : :::.:::::::::::::.:  :::::::::
AGAAAGCTCACTCCCCTCTAAGGAGGCTCTTGAACCCTCTGGAGAGAACGTCATCCAAAA
 1020      1030      1040      1050      1060      1070

      820       830       840       850       860       870
CAAGGAGAACGCAGGTTGATGCAAGAGGTGGAAATGTTCTCCCATATCAAGATGCGACCC
:::.:::::.:::::::::::::::::::::::::::::::::: :::::::::::: :.:::
CAAAGAGAGCACAGGTTGATGCAAGAGGTGGAAATGTTCTCC-ATATCAAGATGTGGCCC
 1080      1090      1100      1110      1120      1130

      880       890       900       910       920       930
AAGGGGCTAAGTGGGAACAGTGGTTATGTGGACTCGTAAGATTCACAGAGAATGTGTGCT
:::::: :::::::::::::: .::::: :::::: : ::::: :::::::: :: .:::
AAGGGGTTAAGTGGGAACAATCATTATACGGACTCTTCAGATTTACAGAGAACTTACACT
 1140      1150      1160      1170      1180      1190
```

FIG 34 (2 OF 6)

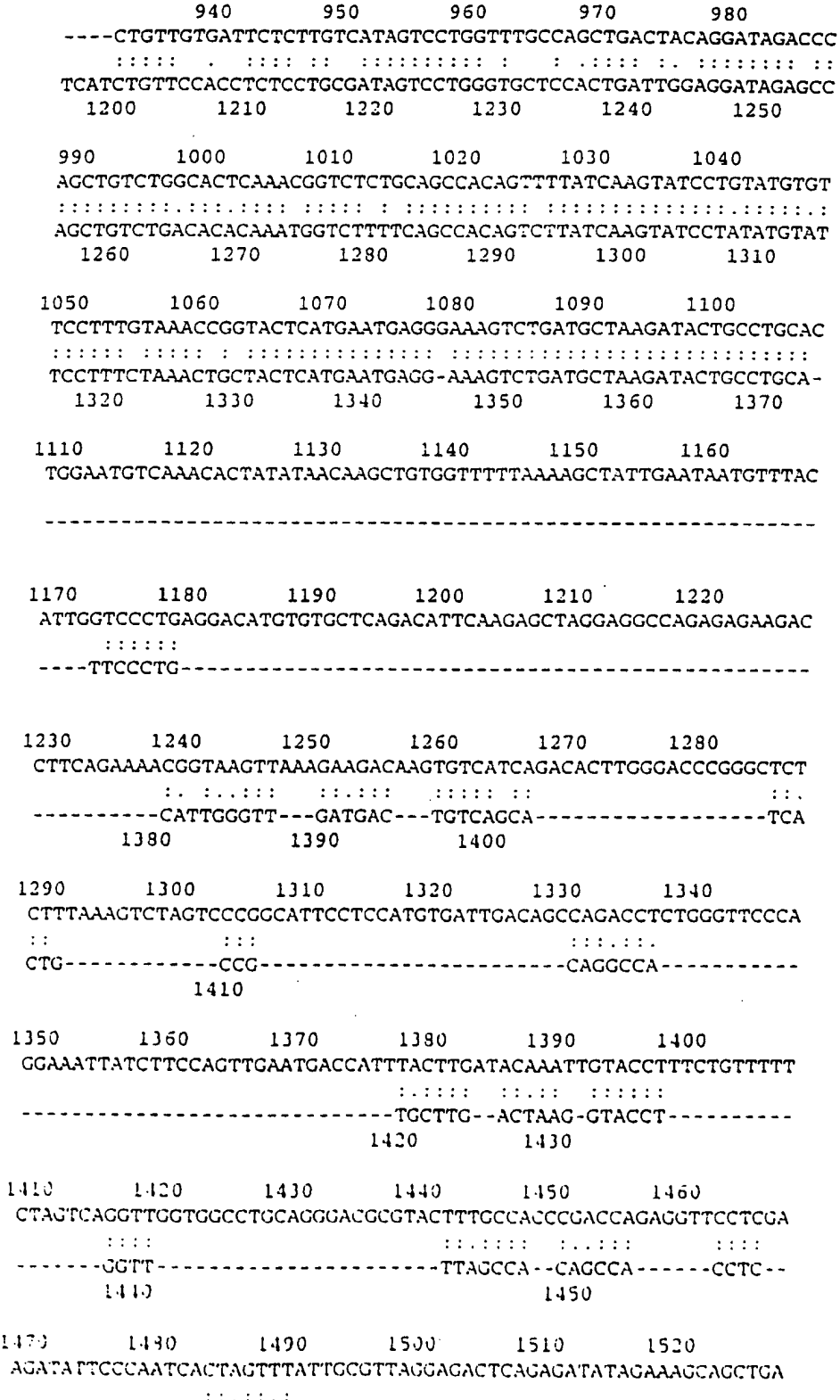

940 950 960 970 980
----CTGTTGTGATTCTCTTGTCATAGTCCTGGTTTGCCAGCTGACTACAGGATAGACCC
TCATCTGTTCCACCTCTCCTGCGATAGTCCTGGGTGCTCCACTGATTGGAGGATAGAGCC
1200 1210 1220 1230 1240 1250
990 1000 1010 1020 1030 1040
AGCTGTCTGGCACTCAAACGGTCTCTGCAGCCACAGTTTTATCAAGTATCCTGTATGTGT
AGCTGTCTGACACACAAATGGTCTTTTCAGCCACAGTCTTATCAAGTATCCTATATGTAT
1260 1270 1280 1290 1300 1310
1050 1060 1070 1080 1090 1100
TCCTTTGTAAACCGGTACTCATGAATGAGGGAAAGTCTGATGCTAAGATACTGCCTGCAC
TCCTTTCTAAACTGCTACTCATGAATGAGG-AAAGTCTGATGCTAAGATACTGCCTGCA-
1320 1330 1340 1350 1360 1370
1110 1120 1130 1140 1150 1160
TGGAATGTCAAACACTATATAACAAGCTGTGGTTTTTAAAAGCTATTGAATAATGTTTAC
1170 1180 1190 1200 1210 1220
ATTGGTCCCTGAGGACATGTGTGCTCAGACATTCAAGAGCTAGGAGGCCAGAGAGAAGAC
----TTCCCTG----------
1230 1240 1250 1260 1270 1280
CTTCAGAAAACGGTAAGTTAAAGAAGACAAGTGTCATCAGACACTTGGGACCCGGGCTCT
----------CATTGGGTT---GATGAC---TGTCAGCA----------TCA
1380 1390 1400
1290 1300 1310 1320 1330 1340
CTTTAAAGTCTAGTCCCGGCATTCCTCCATGTGATTGACAGCCAGACCTCTGGGTTCCCA
CTG----------CCG----------CAGGCCA----------
1410
1350 1360 1370 1380 1390 1400
GGAAATTATCTTCCAGTTGAATGACCATTTACTTGATACAAATTGTACCTTTCTGTTTTT
----------TGCTTG--ACTAAG-GTACCT----------
1420 1430
1410 1420 1430 1440 1450 1460
CTAGTCAGGTTGGTGGCCTGCAGGGACGCGTACTTTGCCACCCGACCAGAGGTTCCTCGA
-------GGTT----------TTAGCCA--CAGCCA------CCTC--
1440 1450
1470 1480 1490 1500 1510 1520
AGATATTCCCAATCACTAGTTTATTGCGTTAGGAGACTCAGAGATATAGAAAGCAGCTGA

FIG 34 (3 OF 6)

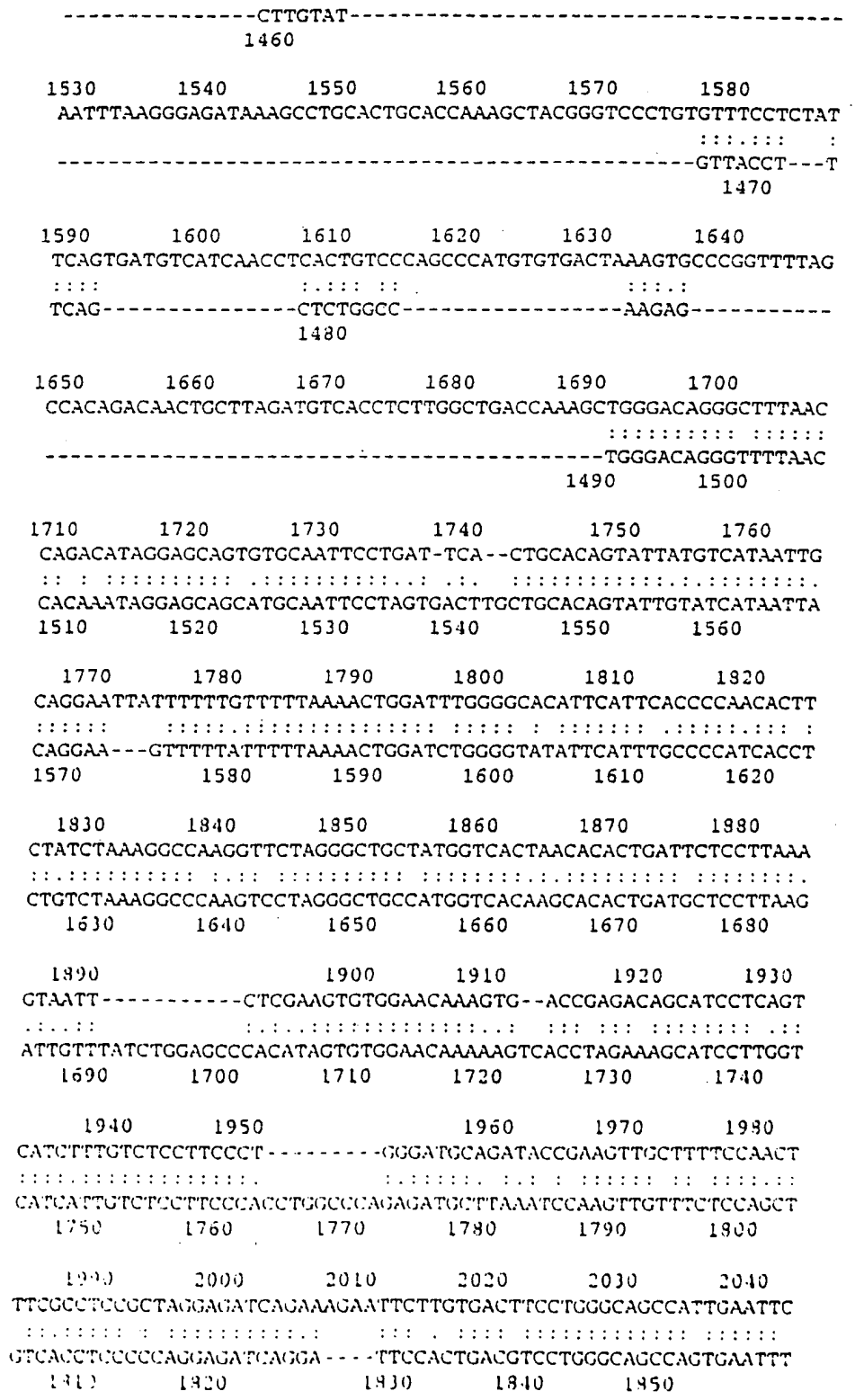

----------CTTGTAT----------
1460
1530 1540 1550 1560 1570 1580
AATTTAAGGGAGATAAAGCCTGCACTGCACCAAAGCTACGGGTCCCTGTGTTTCCTCTAT
GTTACCT---T
1470
1590 1600 1610 1620 1630 1640
TCAGTGATGTCATCAACCTCACTGTCCCAGCCCATGTGTGACTAAAGTGCCCGGTTTTAG
TCAG----------CTCTGGCC----------AAGAG----------
1480
1650 1660 1670 1680 1690 1700
CCACAGACAACTGCTTAGATGTCACCTCTTGGCTGACCAAAGCTGGGACAGGGCTTTAAC
TGGGACAGGGTTTTAAC
1490 1500
1710 1720 1730 1740 1750 1760
CAGACATAGGAGCAGTGTGCAATTCCTGAT-TCA--CTGCACAGTATTATGTCATAATTG
CACAAATAGGAGCAGCATGCAATTCCTAGTGACTTGCTGCACAGTATTGTATCATAATTA
1510 1520 1530 1540 1550 1560
1770 1780 1790 1800 1810 1820
CAGGAATTATTTTTTGTTTTTAAAACTGGATTTGGGGCACATTCATTCACCCCAACACTT
CAGGAA---GTTTTTATTTTTAAAACTGGATCTGGGGTATATTCATTTGCCCCATCACCT
1570 1580 1590 1600 1610 1620
1830 1840 1850 1860 1870 1880
CTATCTAAAGGCCAAGGTTCTAGGGCTGCTATGGTCACTAACACACTGATTCTCCTTAAA
CTGTCTAAAGGCCCAAGTCCTAGGGCTGCCATGGTCACAAGCACACTGATGCTCCTTAAG
1630 1640 1650 1660 1670 1680
1890 1900 1910 1920 1930
GTAATT----------CTCGAAGTGTGGAACAAAGTG--ACCGAGACAGCATCCTCAGT
ATTGTTTATCTGGAGCCCACATAGTGTGGAACAAAAAGTCACCTAGAAAGCATCCTTGGT
1690 1700 1710 1720 1730 1740
1940 1950 1960 1970 1980
CATCTTTGTCTCCTTCCCT---------GGGATGCAGATACCGAAGTTGCTTTTCCAACT
CATCATTGTCTCCTTCCCACCTGGCCCAGAGATGCTTAAATCCAAGTTGTTTCTCCAGCT
1750 1760 1770 1780 1790 1800
1990 2000 2010 2020 2030 2040
TTCGCCTCCGCTAGGAGATCAGAAAGAATTCTTGTGACTTCCTGGGCAGCCATTGAATTC
GTCACCTCCCCCAGGAGATCAGGA----TTCCACTGACGTCCTGGGCAGCCAGTGAATTT
1810 1820 1830 1840 1850

FIG 34 (4 OF 6)

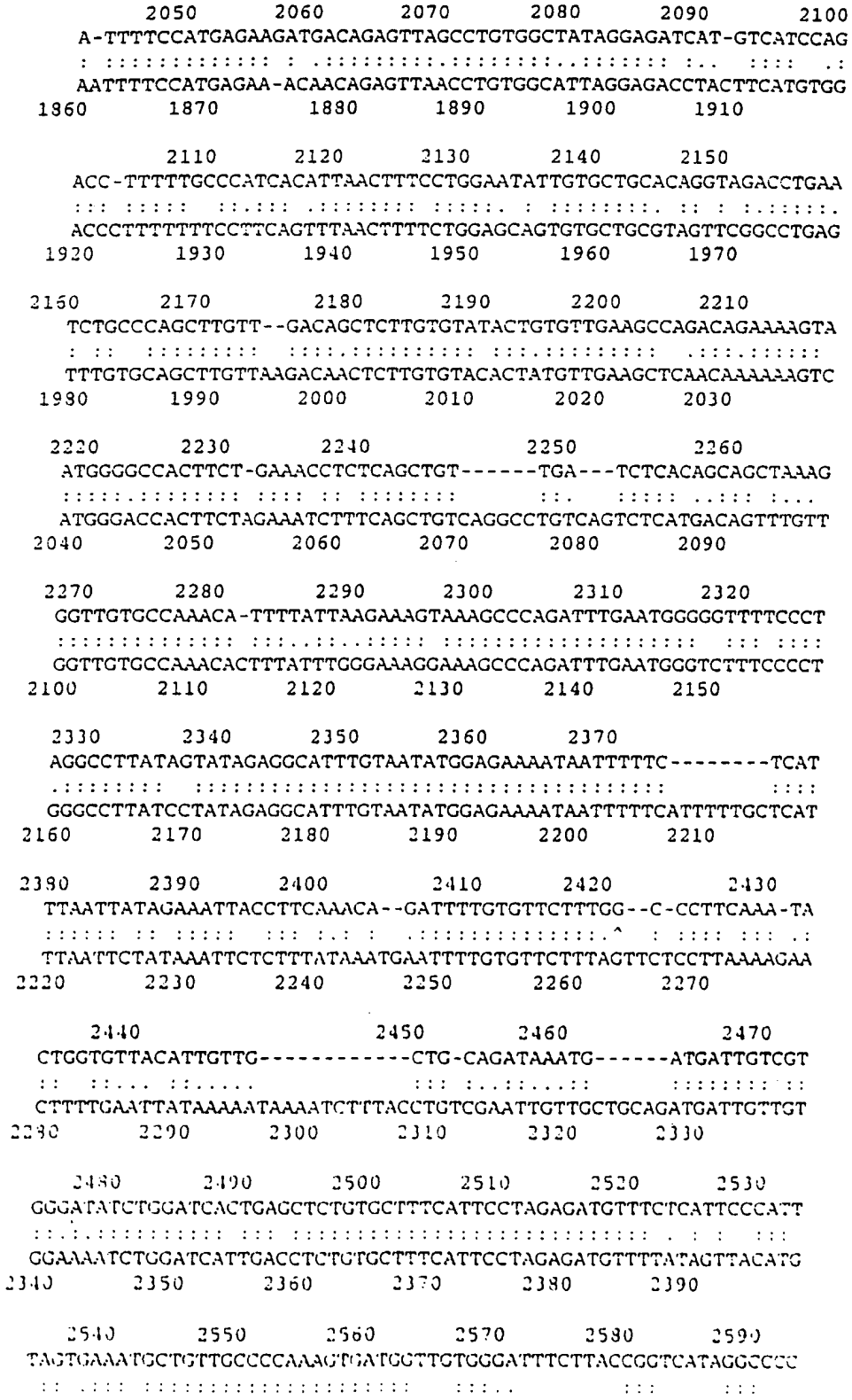


FIG 34 (5 OF 6)

```
     -AGCAAAA-GCTGTTGCCCCAAAGTGATGGCCCTGGAGG-------CGG-----GGC---
    2400       2410       2420       2430                   2440

        2600       2610       2620       2630       2640       2650
     GGTGAGGAGCAGGGAAGCGCCATTGTGAAAGATTAAAGAAAGCACTTCCACTTGAGCTCC
       ::::::.:::::::. :::. :::::::.  :::::    :::::::  .:::.:.::::
     --TGAGGAACAGGGAAATGCCGCTGTGAAGTCTTAAA----GCACTTCTGCTTAAACTCC
            2450       2460       2470           2480       2490

            2660       2670       2680       2690       2700
     TTATG----GAGTGAGCTTCCCTGTGCCCACTCAGTGAACTAAGTCTGACCATCCTTCAG
     .:.::    :::::.:: :::::::::::.:::::   .::.:: :::.::.:: ::::.:
     ATGTGTGAGGAGTGTGCCTCCCTGTGCCCTCTCAGC--TCTGAGGCTGGCCGTCTTTCGG
      2500       2510       2520       2530         2540       2550

2710       2720       2730       2740       2750       2760
   GGACGTTCCTTTTGGTAAATATACACTGTAATCTTTAAGTCTAAATTTATATGTGAAAGT
   ::. :::::::::: :::::::::::::::::::: .:::::::::::::::::: .::.:
   GGT-GTTCCTTTTGGCAAATATACACTGTAATCTT-GAGTCTAAATTTATATGTTGAAAT
       2560       2570       2580       2590       2600       2610

 2770           2780       2790       2800       2810       2820
   --TAACTTTTTT----TAAAAACCTAAATAAAATTATTTTCCTATCAAAAAAAAAAAAAAA
     :: :::::::     :::.:: ::::::::::::::::: ::::::::::::::::::
   GCTACCTTTTTTAAAATAAGAAACTAAATAAAATTATTTTACTATCAAAAAAAAAAAAAAA
        2620       2630       2640       2650       2660       2670

     2830
   AAAGGGCGGCC
   ::::..      v
   AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
        2680       2690       2700
```

FIG 34 (6 OF 6)

```
                10         20         30         40         50
HUMAN     GTCGACCCACGCGTCCGGCGGGGACAACTGGGTCTTTTGCGGCTGCAGC-GGGCTTGTAG
          :::::::::::::::::::     :..:::. ::. : ::::::::.:: :.:::::: ::
MURINE    GTCGACCCACGCGTCCGGC-----CTGCTGA-TCAGTGGCGGCTGCGGCTGAGCTTGCAG
                10              20         30         40         50

          60         70         80         90        100        110
          GTGTCCGGCTTTGCTGGCCCAGCAAGCCTGATAAGCATGAAGCTCTTATCTTTGGTGGCT
          : .:: .:  :::::::: ::::::::: ::::::::::::::  :.: ::::::::::
          GCATCTAGTCTTGCTGGCTCAGCAAGCCCGATAAGCATGAAGCTGCTGTGTTTGGTGGCT
              60         70         80         90        100        110

         120        130        140        150        160        170
          GTGGTCGGGTGTTTGCTGGTGCCCCCAGCTGAAGCCAACAAGAGTTCTGAAGATATCCGG
          ::::: ::::: ::::::::::::::::: ::::::::::::: :::::::::::::::
          GTGGTGGGGTGCTTGCTGGTGCCCCCAGCTCAAGCCAACAAGAGCTCTGAAGATATCCGG
             120        130        140        150        160        170

         180        190        200        210        220        230
          TGCAAATGCATCTGTCCACCTTATAGAAACATCAGTGGGCACATTTACAACCAGAATGTA
          ::::::::::::::::::::.:::::: :::::::::::: :::::::::::::::::::::::.
          TGCAAATGCATCTGTCCGCCTTACAGAAACATCAGCGGGCACATTTACAACCAGAATGTG
             180        190        200        210        220        230

         240        250        260        270        280        290
          TCCCAGAAGGACTGCAACTGCCTGCACGTGGTGGAGCCCATGCCAGTGCCTGGCCATGAC
          :: ::::::::::::::::::::::::: :::::::::::::::::::::::::::::: ::
          TCTCAGAAGGACTGCAACTGCCTGCATGTGGTGGAGCCCATGCCAGTGCCTGGCCACGAT
             240        250        260        270        280        290

         300        310        320        330        340        350
          GTGGAGGCCTACTGCCTGCTGTGCGAGTGCAGGTACGAGGAGCGCAGCACCACCACCATC
          :::::.:::::::::::::::: :::::::: :::::::::::::: :::::::: ::::::
          GTGGAAGCCTACTGCCTGCTCTGCGAGTGTAGGTACGAGGAGCGTAGCACCACAACCATC
             300        310        320        330        340        350

         360        370        380        390        400        410
          AAGGTCATCATTGTCATCTACCTGTCCGTGGTGGGTGCCCTGTTGCTCTACATGGCCTTC
          :::::::: ::::::::::::::::: :::::::: ::::: ::.:::::::::::::::::
          AAGGTCATTATTGTCATCTACCTGTCTGTGGTGGGGGCCCTCTTACTCTACATGGCCTTC
             360        370        380        390        400        410

         420        430        440        450        460        470
          CTGATGCTGGTGGACCCTCTGATCCGAAAGCCGGATGCATACACTGAGCAACTGCACAAT
          ::::::::::::::::: :: ::::::.:::::.::::: :: ::::::::::.:::::::
          CTGATGCTGGTGGACCCGCTCATCCGGAAGCCAGATGCCTATACTGAGCAGCTGCACAAT
             420        430        440        450        460        470

         480        490        500        510        520        530
          GAGGAGGAGAATGAGGATGCTGGCTCTATGGCAGCAGCTGCTGCATCCCTCGGGGGACCC
```

FIG 35 (1 OF 3)

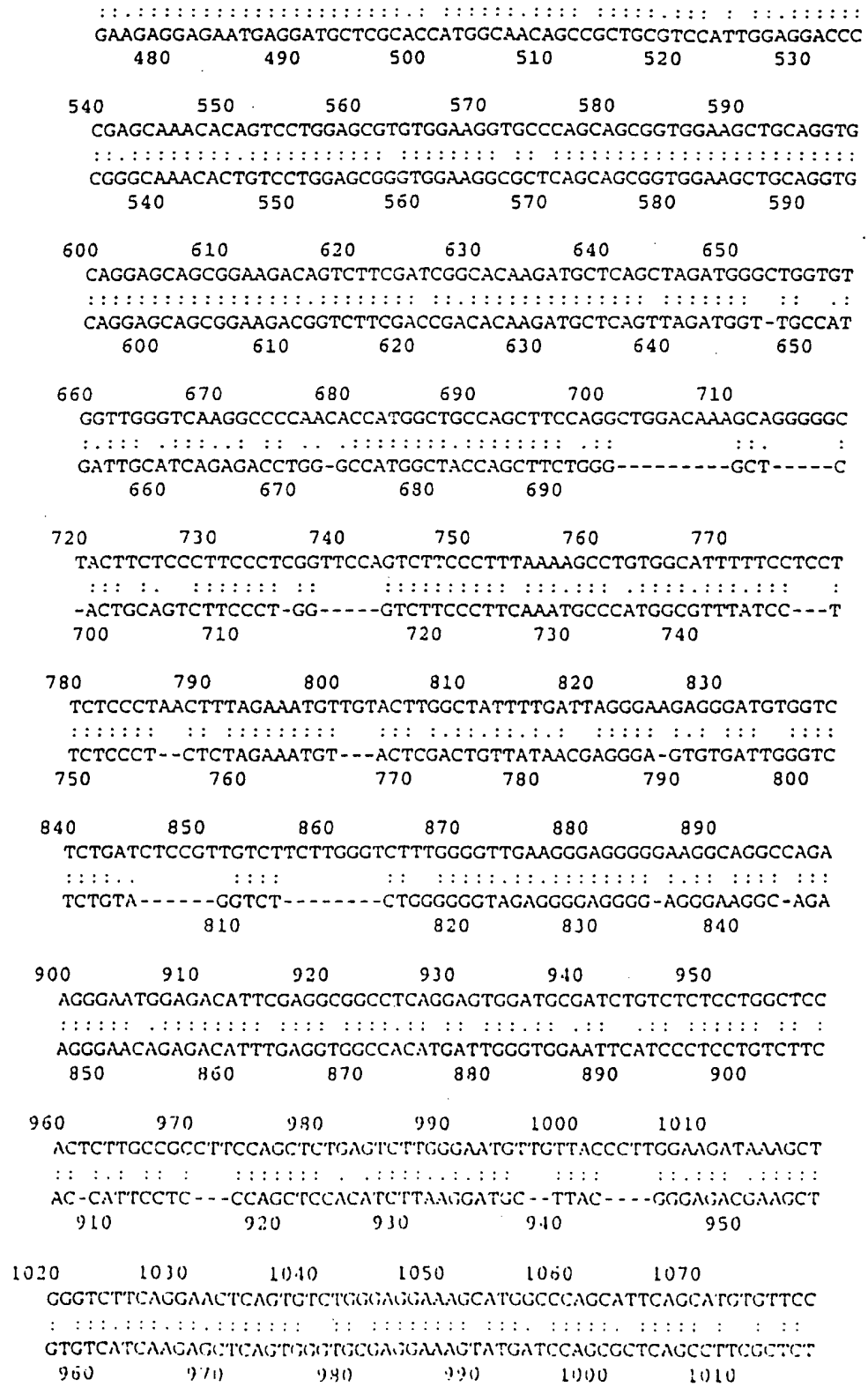


FIG 3S (2 OF 3)

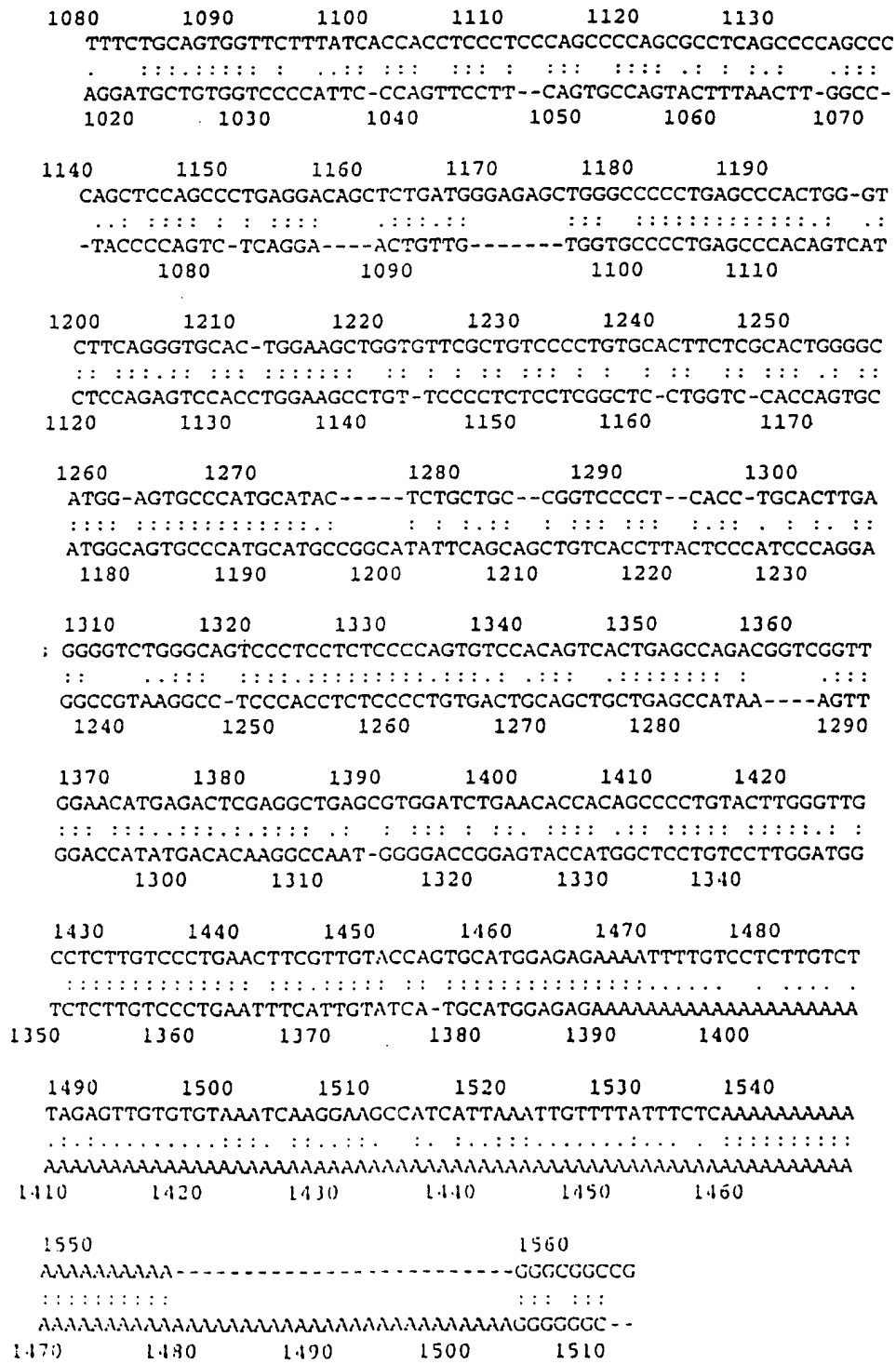

1080 1090 1100 1110 1120 1130
TTTCTGCAGTGGTTCTTTATCACCACCTCCCTCCCAGCCCCAGCGCCTCAGCCCCAGCCC
AGGATGCTGTGGTCCCCATTC-CCAGTTCCTT--CAGTGCCAGTACTTTAACTT-GGCC-
1020 1030 1040 1050 1060 1070
1140 1150 1160 1170 1180 1190
CAGCTCCAGCCCTGAGGACAGCTCTGATGGGAGAGCTGGGCCCCCTGAGCCCACTGG-GT
-TACCCCAGTC-TCAGGA----ACTGTTG-------TGGTGCCCCTGAGCCCACAGTCAT
1080 1090 1100 1110
1200 1210 1220 1230 1240 1250
CTTCAGGGTGCAC-TGGAAGCTGGTGTTCGCTGTCCCCTGTGCACTTCTCGCACTGGGGC
CTCCAGAGTCCACCTGGAAGCCTGT-TCCCCTCTCCTCGGCTC-CTGGTC-CACCAGTGC
1120 1130 1140 1150 1160 1170
1260 1270 1280 1290 1300
ATGG-AGTGCCCATGCATAC-----TCTGCTGC--CGGTCCCCT--CACC-TGCACTTGA
ATGGCAGTGCCCATGCATGCCGGCATATTCAGCAGCTGTCACCTTACTCCCATCCCAGGA
1180 1190 1200 1210 1220 1230
1310 1320 1330 1340 1350 1360
GGGGTCTGGGCAGTCCCTCCTCTCCCCAGTGTCCACAGTCACTGAGCCAGACGGTCGGTT
GGCCGTAAGGCC-TCCCACCTCTCCCCTGTGACTGCAGCTGCTGAGCCATAA----AGTT
1240 1250 1260 1270 1280 1290
1370 1380 1390 1400 1410 1420
GGAACATGAGACTCGAGGCTGAGCGTGGATCTGAACACCACAGCCCCTGTACTTGGGTTG
GGACCATATGACACAAGGCCAAT-GGGGACCGGAGTACCATGGCTCCTGTCCTTGGATGG
1300 1310 1320 1330 1340
1430 1440 1450 1460 1470 1480
CCTCTTGTCCCTGAACTTCGTTGTACCAGTGCATGGAGAGAAAATTTTGTCCTCTTGTCT
TCTCTTGTCCCTGAATTTCATTGTATCA-TGCATGGAGAGAAAAAAAAAAAAAAAAAAAA
1350 1360 1370 1380 1390 1400
1490 1500 1510 1520 1530 1540
TAGAGTTGTGTGTAAATCAAGGAAGCCATCATTAAATTGTTTTATTTCTCAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
1410 1420 1430 1440 1450 1460
1550 1560
AAAAAAAAAA----------GGGCGGCCG
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGGGGGGC--
1470 1480 1490 1500 1510

FIG 3F (3 OF 3)

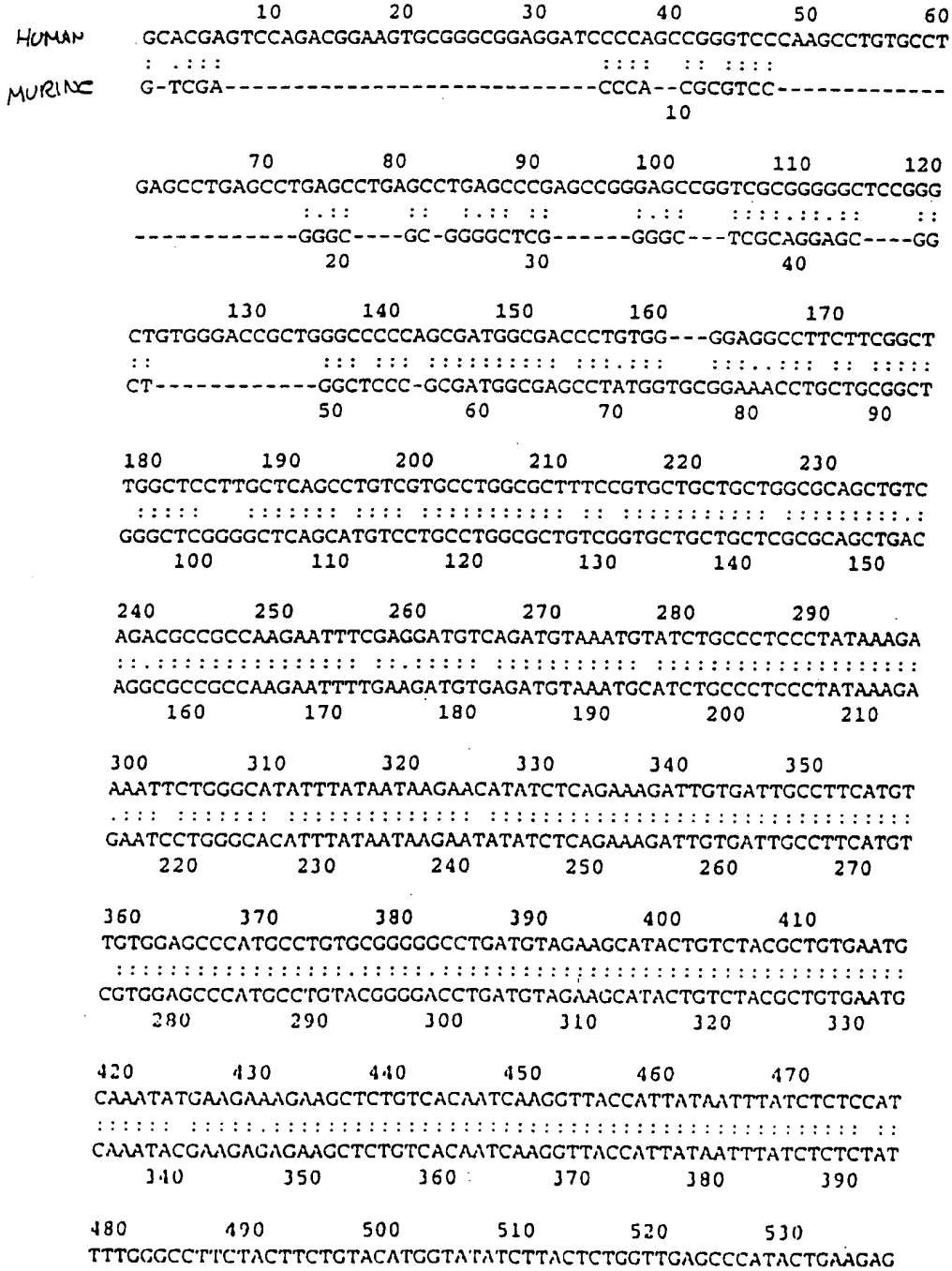

HUMAN
MURINE
GCACGAGTCCAGACGGAAGTGCGGGCGGAGGATCCCCAGCCGGGTCCCAAGCCTGTGCCT
G-TCGA----------CCCA--CGCGTCC----------
GAGCCTGAGCCTGAGCCTGAGCCTGAGCCCGAGCCGGGAGCCGGTCGCGGGGGCTCCGGG
----------GGGC----GC-GGGGCTCG------GGGC---TCGCAGGAGC----GG
CTGTGGGACCGCTGGGCCCCCAGCGATGGCGACCCTGTGG---GGAGGCCTTCTTCGGCT
CT----------GGCTCCC-GCGATGGCGAGCCTATGGTGCGGAAACCTGCTGCGGCT
TGGCTCCTTGCTCAGCCTGTCGTGCCTGGCGCTTTCCGTGCTGCTGCTGGCGCAGCTGTC
GGGCTCGGGGCTCAGCATGTCCTGCCTGGCGCTGTCGGTGCTGCTGCTCGCGCAGCTGAC
AGACGCCGCCAAGAATTTCGAGGATGTCAGATGTAAATGTATCTGCCCTCCCTATAAAGA
AGGCGCCGCCAAGAATTTTGAAGATGTGAGATGTAAATGCATCTGCCCTCCCTATAAAGA
AAATTCTGGGCATATTTATAATAAGAACATATCTCAGAAAGATTGTGATTGCCTTCATGT
GAATCCTGGGCACATTTATAATAAGAATATATCTCAGAAAGATTGTGATTGCCTTCATGT
TGTGGAGCCCATGCCTGTGCGGGGGCCTGATGTAGAAGCATACTGTCTACGCTGTGAATG
CGTGGAGCCCATGCCTGTACGGGGACCTGATGTAGAAGCATACTGTCTACGCTGTGAATG
CAAATATGAAGAAAGAAGCTCTGTCACAATCAAGGTTACCATTATAATTTATCTCTCCAT
CAAATACGAAGAGAGAAGCTCTGTCACAATCAAGGTTACCATTATAATTTATCTCTCTAT
TTTGGGCCTTCTACTTCTGTACATGGTATATCTTACTCTGGTTGAGCCCATACTGAAGAG

FIG 3C (1 of 4)

```
:::::::::::::.:::::::::::::::::::::::::  :.:::::::::::: ::::::::
TTTGGGCCTTCTGCTTCTGTACATGGTATATCTTACCTTAGTTGAGCCCATCCTGAAGAG
      400       410       420       430       440       450

    540       550       560       570       580       590
GCGCCTCTTTGGACATGCACAGTTGATACAGAGTGATGATGATATTGGGGATCACCAGCC
::::::::::::::::  : ::: ::.:.::::: :::::::: .:::::::::::::::::
GCGCCTCTTTGGACACTCCCAGCTGTTGCAGAGCGATGATGACGTTGGGGATCACCAGCC
      460       470       480       490       500       510

    600       610       620       630       640       650
TTTTGCAAATGCACACGATGTGCTAGCCCGCTCCCGCAGTCGAGCCAACGTGCTGAACAA
:::::::::::: :: ::::::::.:::::::: ::::: :::::::: :: ::.:::::
TTTTGCAAATGCCCATGATGTGCTGGCCCGCTCTCGCAGCCGAGCCAATGTTCTAAACAA
      520       530       540       550       560       570

    660       670       680       690       700       710
GGTAGAATATGCACAGCAGCGCTGGAAGCTTCAAGTCCAAGAGCAGCGAAAGTCTGTCTT
:::.::.:: ::.:::::::::::::::::: ::.::::::.::::::::::::::::::
GGTGGAGTACGCTCAGCAGCGCTGGAAGCTCCAGGTCCAGGAGCAGCGAAAGTCTGTCTT
      580       590       600       610       620       630

    720       730       740       750       760       770
TGACCGGCATGTTGTCCTCAGCTAATTGGGAATTGAATTCAAGGTGACTAGAAAGAAACA
 :::::.:: ::::::::::::::: :::::: ::.:.::: ::::::::::.:::: ::
CGACCGACACGTTGTCCTCAGCTAACTGGGAACTGGAATCA-GGTGACTAGGAAGAA-CA
      640       650       660       670       680       690

    780       790       800       810       820       830
GGCAGACAACTGGAAAGAACTGACTGGGTTTTGCTGGGTTTCATTTTAATACCTTGTTGA
:::::::::::::.::::: ::.::::::: :   : : :   :.::::::::.::.:::: .
CGCAGACAACTGGGAAGAATTGTCTGGGTGT--CCGTG---CGTTTTAATGCCATGTTTG
      700       710       720             730       740

    840                 850       860       870       880
TTT---CA---CCAA-CTG-TTGCTGGAAGATTCAAAACTGGAAGCAAAAAC-TTGCTTG
:::   ::   ::.. ::: .:: .:::::: :: :::::::::::::::  : .::::::
TTTTTACAAATCCTTGCTGGATGGAGGAAGACTCCAAACTGGAAGCAAACCCCATGCTTG
  750       760       770       780       790       800

    890       900       910       920       930       940
ATTTTTTTTTCTTGTTAACGTAATAATAGAGACATTTTTAAAAGCACACAGCTCAAAGTC
.:.::::     : :::::: .::.::::::::::::::::::: : ::::::::: :: :::::
GTATTTT---CCTGTTAATATATTAATAGAGACATTTTTACA-GCACACAGTTCCAAGTC
  810                 820       830       840       850       860

    950       960       970       980       990      1000
AGCCAATAAGTCTTTTCCTATTTGTGACTTTTACTAATAAAAATAAATCTGCCTGTAAAT
:.:::.:::::::::::::::: :::::::::::::::::::::.:::. :::::::::.:.:
AACCAGTAAGTCTTTTCCTACTTGTGACTTTTACTAATAAAATTAAG-CTGCCTGTGAGT
      870       880       890       900       910       920

   1010      1020      1030      1040      1050      1060
TATCTDGAAGTCCTTTACCTGGAACAAGCACTCTCTTTTTCACCAC-CA-TCCT--CTTT
::::: :::: ::   :.:::::::::::::::.:::::::: : .:::: :: : ::  :::
TATCTTGAAGCCCCGTGCCTGGAACAAGCTCTCTCTTTCTTGCCACACAGTTCTAACTTG
      930       940       950       960       970       980
```

FIG 36 (2 of 4)

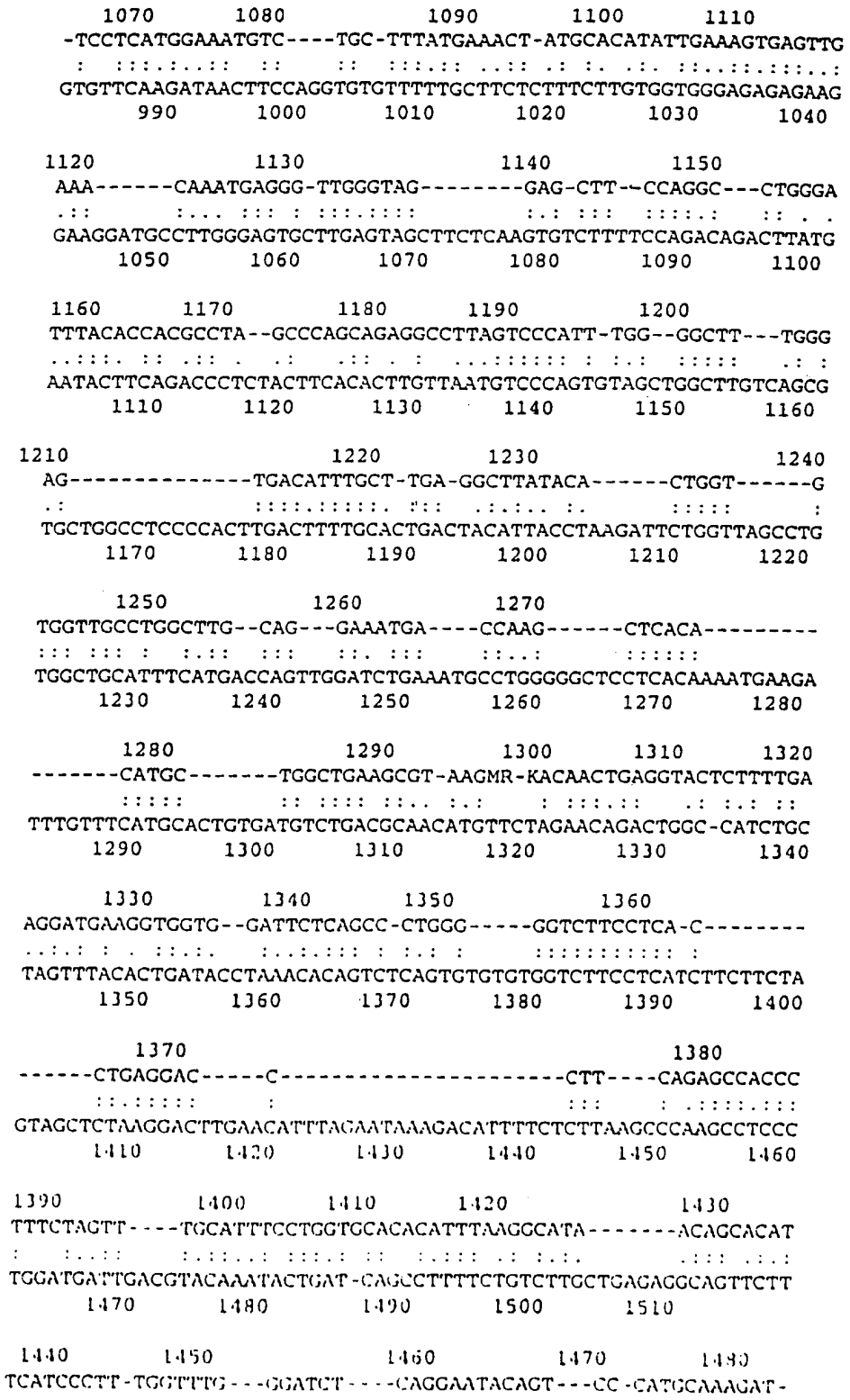


FIG 3G (3 OF 4)

```
    : :.:  .: :::  .:    ::.:.    :..::.:.:::.   :: :.  :..:::.
    TGAACTGATGTGGGCAGCTTTGAACAAGGACTAGAGTTCAGATTGCCTCTCTCTGAGAAG
1520       1530       1540       1550       1560       1570

        1490       1500       1510       1520       1530       1540
    TCTCTGGTTTTATGGCTTTTTTCCCTTTCT-TTACACCATCCTCTCCCATAAGCACCCAT
    ::: . . ::.::: :.. :  : ::: : :: :. ::::::::   ..:.: : : ::
    TCTAACAGTTATTGGATAACTGGCTTTTTTCTTCCTACATCCTCTTTGGAATGTAACAAT
1580       1590       1600       1610       1620       1630

         1550       1560       1570
    GTCTTTGAATATGAATGTATTTGTAAAATAAAAAA-------
    .. .:.....:: .::.   ..........:.:::..
    AAAATAATTTACAAAACCCAAAAAAAAAAAAAAAGGGCGGCCG
1640       1650       1660       1670       1680
```

FIG 3G (4 OF 4)

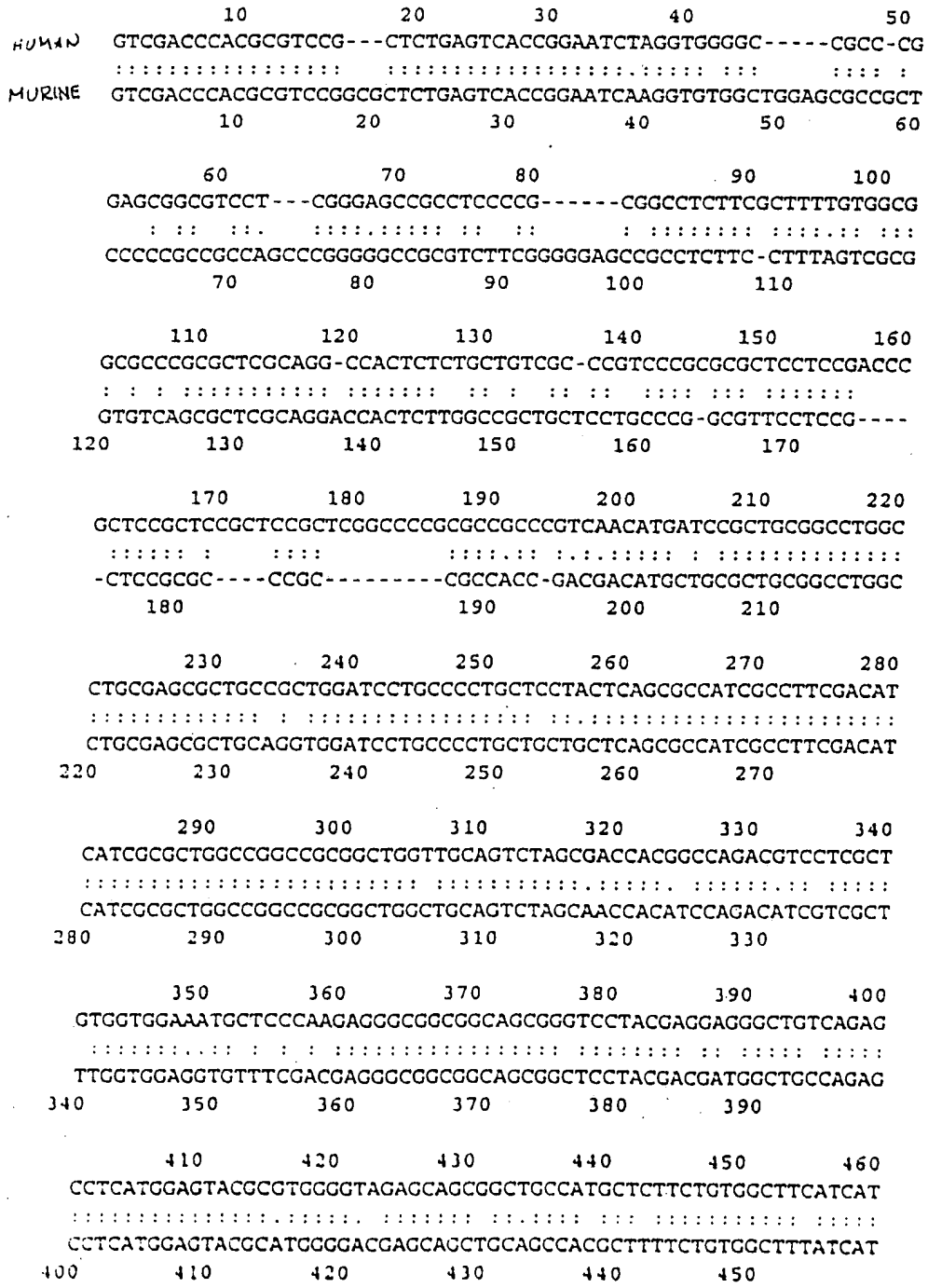


FIG 37 (10F4)

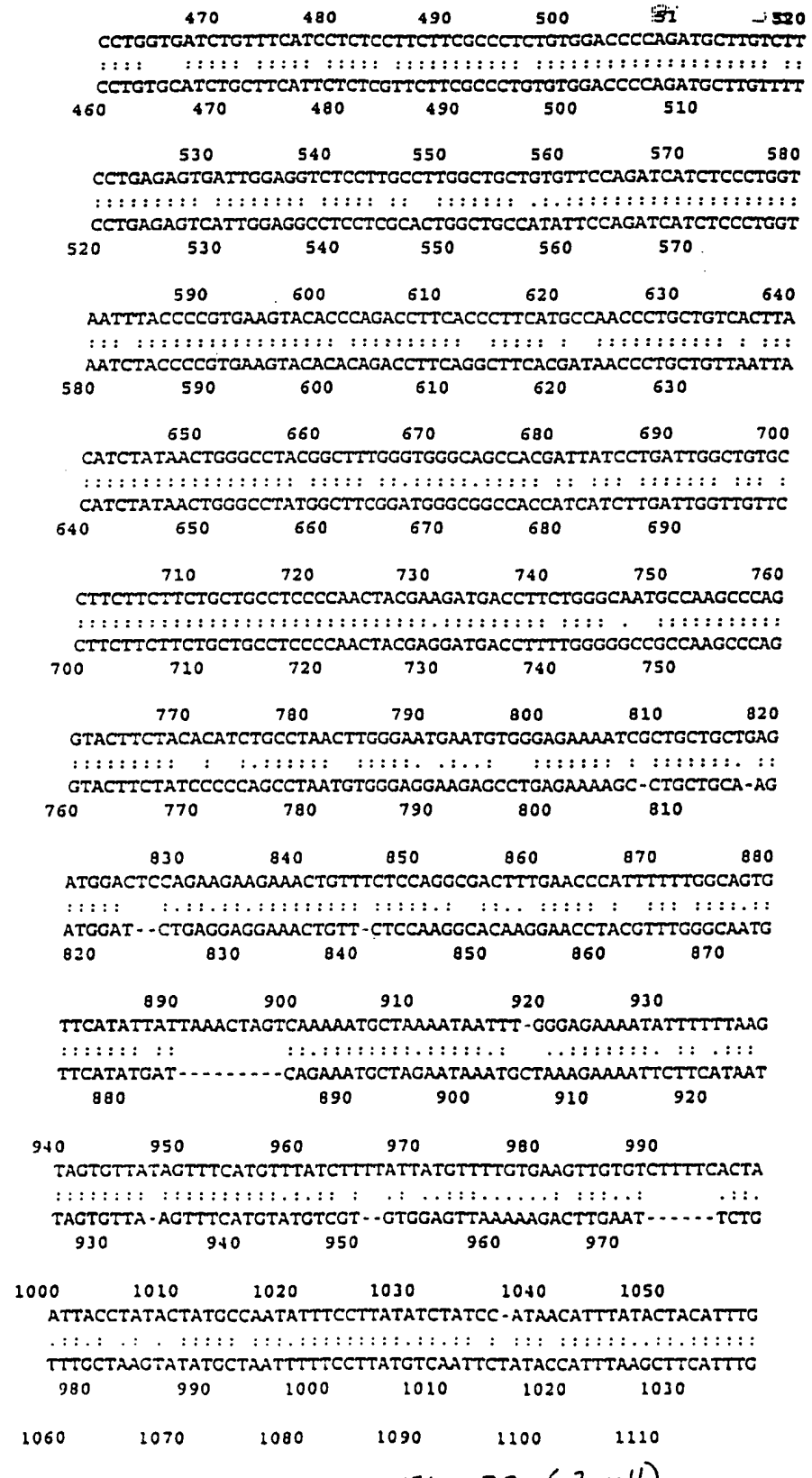


FIG 37 (2 or 4)

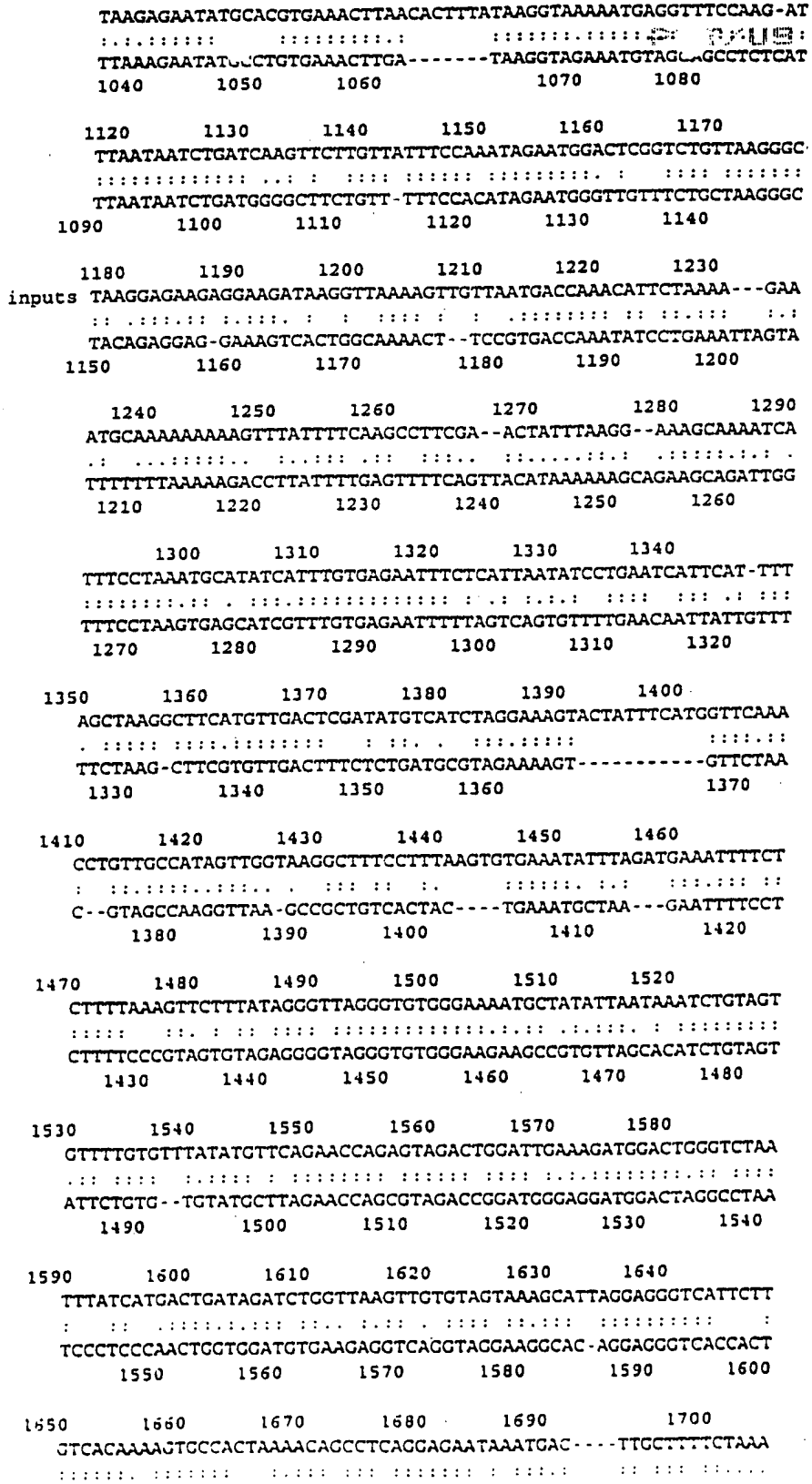


FIG 37 (3 of 4)

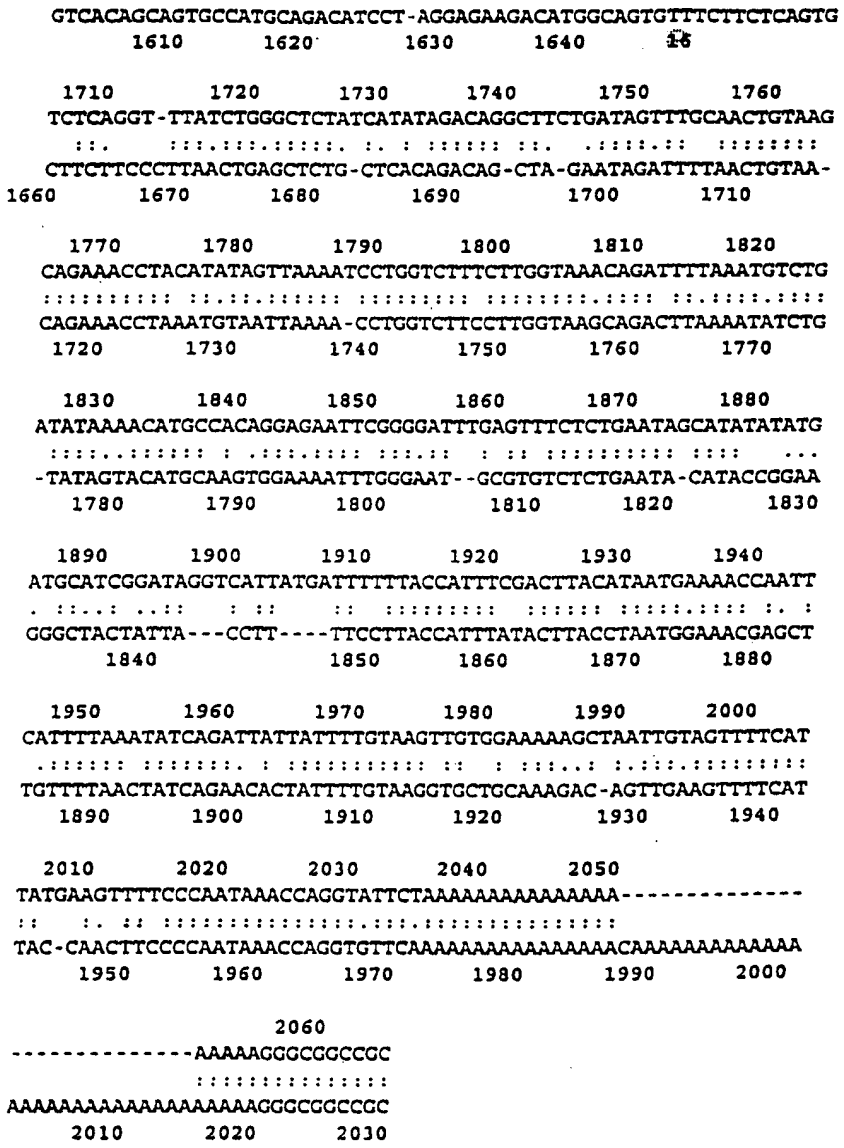

GTCACAGCAGTGCCATGCAGACATCCT-AGGAGAAGACATGGCAGTGTTTCTTCTCAGTG
1610 1620 1630 1640 16
1710 1720 1730 1740 1750 1760
TCTCAGGT-TTATCTGGGCTCTATCATATAGACAGGCTTCTGATAGTTTGCAACTGTAAG
CTTCTTCCCTTAACTGAGCTCTG-CTCACAGACAG-CTA-GAATAGATTTTAACTGTAA-
1660 1670 1680 1690 1700 1710
1770 1780 1790 1800 1810 1820
CAGAAACCTACATATAGTTAAAATCCTGGTCTTTCTTGGTAAACAGATTTTAAATGTCTG
CAGAAACCTAAATGTAATTAAAA-CCTGGTCTTCCTTGGTAAGCAGACTTAAAATATCTG
1720 1730 1740 1750 1760 1770
1830 1840 1850 1860 1870 1880
ATATAAAACATGCCACAGGAGAATTCGGGGATTTGAGTTTCTCTGAATAGCATATATATG
-TATAGTACATGCAAGTGGAAAATTTGGGAAT--GCGTGTCTCTGAATA-CATACCGGAA
1780 1790 1800 1810 1820 1830
1890 1900 1910 1920 1930 1940
ATGCATCGGATAGGTCATTATGATTTTTTACCATTTCGACTTACATAATGAAAACCAATT
GGGCTACTATTA---CCTT----TTCCTTACCATTTATACTTACCTAATGGAAACGAGCT
1840 1850 1860 1870 1880
1950 1960 1970 1980 1990 2000
CATTTTAAATATCAGATTATTATTTTGTAAGTTGTGGAAAAAGCTAATTGTAGTTTTCAT
TGTTTTAACTATCAGAACACTATTTTGTAAGGTGCTGCAAAGAC-AGTTGAAGTTTTCAT
1890 1900 1910 1920 1930 1940
2010 2020 2030 2040 2050
TATGAAGTTTTCCCAATAAACCAGGTATTCTAAAAAAAAAAAAAAA----------
TAC-CAACTTCCCCAATAAACCAGGTGTTCAAAAAAAAAAAAAAAAAACAAAAAAAAAAAAA
1950 1960 1970 1980 1990 2000
2060
----------AAAAAGGGCGGCCGC
AAAAAAAAAAAAAAAAAAAAGGGCGGCCGC
2010 2020 2030

FIG 37 (4 OF 4)

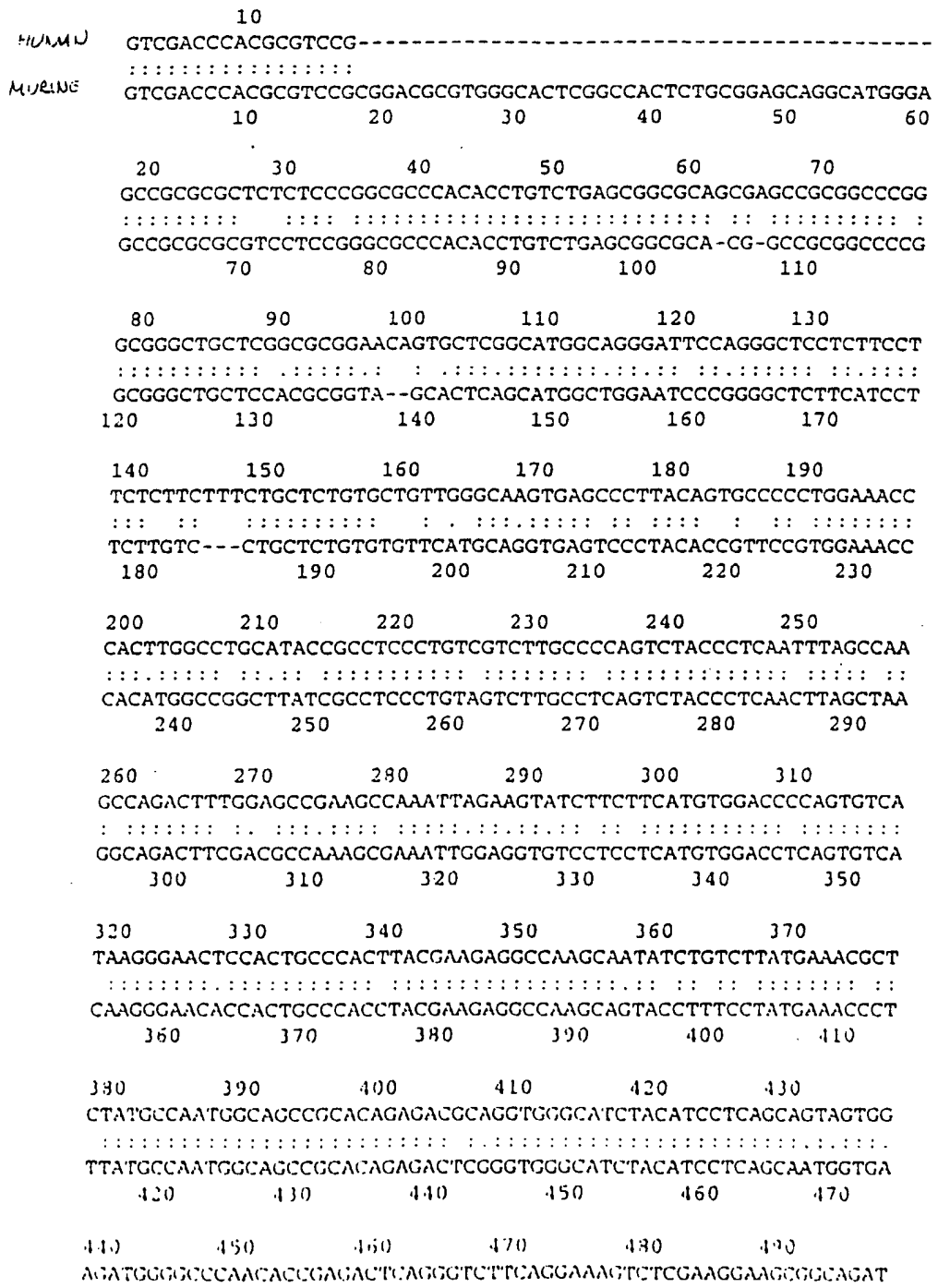


FIG 3E (1 OF 7)

```
::. .:::: :.: .: :::::::.:.: : .::::.:.::::: :::::: :::::::
AGGCAGGGCACGAGGCAGAGACTCGGAGGCCACAGGGAGATCTCGCAGGAAGAGGCAGAT
     480       490       500       510       520       530

500       510       520       530       540       550
TTATGGCTATGACAGCAGGTTCAGCATTTTTGGGAAGGACTTCCTGCTCAACTACCCTTT
::::::::: :: .::::::: ::::::::::::::::::::::::::::: :: :::::
TTATGGCTACGATGGCAGGTTTAGCATTTTTGGGAAGGACTTCCTGCTCAATTATCCTTT
     540       550       560       570       580       590

560       570       580       590       600       610
CTCAACATCAGTGAAGTTATCCACGGGCTGCACCGGCACCCTGGTGGCAGAGAAGCATGT
:::::::::.::::::::.:: :: :::::::: ::::::::::::::::::::::: ::
CTCAACATCGGTGAAGTTGTCTACTGGCTGCACTGGCACCCTGGTGGCAGAGAAGCACGT
     600       610       620       630       640       650

620       630       640       650       660       670
CCTCACAGCTGCCCACTGCATACACGATGGAAAAACCTATGTGAAAGGAACCCAGAAGCT
::::::.:::::::::::::::::::::::.:::::::::::::::::.:: :::::.::
CCTCACTGCTGCCCACTGCATACACGATGGGAAAACCTATGTGAAAGGGACACAGAAACT
     660       670       680       690       700       710

680       690       700       710       720       730
TCGAGTGGGCTTCCTAAAGCCCAAGTTTAAAGATGGTGGTCGAGGGGCCAACGACTCCAC
 ::::::::::::::.::::::::::.:::::::::::   .::::: ::::..::: :
CCGAGTGGGCTTCCTGAAGCCCAAGTATAAAGATGGTGCCGAAGGGGACAACAGCTCGAG
     720       730       740       750       760       770

740       750       760       770       780       790
TTCAGCCATGCCCGAGCAGATGAAATTTCAGTGGATCCGGGTGAAACGCACCCATGTGCC
 ::::::::::: ::  :::::::.:::::::::::::: ::::::::::::::::::::
CTCAGCCATGCCAGACAAGATGAAGTTTCAGTGGATCCGCGTGAAACGCACCCATGTGCC
     780       790       800       810       820       830

800       810       820       830       840       850
CAAGGGTTGGATCAAGGGCAATGCCAATGACATCGGCATGGATTATGATTATGCCCTCCT
:::::: ::::::::::::::::::::::::::::::::::::::::: :: ::::: ::
CAAGGGGTGGATCAAGGGCAATGCCAATGACATCGGCATGGATTATGACTACGCCCTGCT
     840       850       860       870       880       890

860       870       880       890       900       910
GGAACTCAAAAAGCCCCACAAGAGAAAATTTATGAAGATTGGGGTGAGCCCTCCTGCTAA
:::::::::.::.::::::::.::: :.:: ::::::::::: ::::: :::::.:: ::
GGAACTCAAGAAACCCCACAAAAGACAGTTCATGAAGATTGGTGTGAGTCCTCCAGCGAA
     900       910       920       930       940       950

920       930       940       950       960       970
GCAGCTGCCAGGGGGCAGAATTCACTTCTCTGGTTATGACAATGACCGACCAGGCAATTT
:::::: :::::::::::.:: ::::::::::::::::::::::::::.:: ::::::::
GCAGCTCCCAGGGGGCAGGATCCACTTCTCTGGTTATGACAATGACCGGCCCGGCAATTT
     960       970       980       990      1000      1010

980       990      1000      1010      1020      1030
GGTGTATCGCTTCTGTGACGTCAAAGACGAGACCTATGACTTGCTCTACCAGCAATGCGA
:::::: ::::::::::: :::::::: :::::::: ::: : :::::::::::.:: ::
GGTGTACCGCTTCTGTGATGTCAAAGATGAGACCTACGACCTTCTCTACCAGCAGTGTGA
    1020      1030      1040      1050      1060      1070
```

FIG 38 (2 of 7)

```
      1040       1050       1060       1070       1080       1090
; TGCCCAGCCAGGGGCCAGCGGGTCTGGGGTCTATGTGAGGATGTGGAAGAGACAGCAGCA
   :::::::: :::::::: :: ::.:::::::::::::::::::::::::::::: .::::: 
  CGCCCAGCCCGGGGCCAGTGGTTCAGGGGTCTATGTGAGGATGTGGAAGAGACCACAGCA
     1080       1090       1100       1110       1120       1130

     1100       1110       1120       1130       1140       1150
; GAAGTGGGAGCGAAAAATTATTGGCATTTTTTCAGGGCACCAGTGGGTGGACATGAATGG
  :::.:::::. :::::::::: ::::: :::::::::::::::::::::::::::::::: 
  GAAATGGGAAAGAAAAATTATCGGCATCTTTTCAGGGCACCAGTGGGTGGACATGAATGG
     1140       1150       1160       1170       1180       1190

     1160       1170       1180       1190       1200       1210
: TTCCCCACAGGATTTCAACGTGGCTGTCAGAATCACTCCTCTCAAATATGCCCAGATTTG
   :: ::::::::::::::::::::.:: :::::::: ::::: ::::::::::::::::: 
  CTCTCCACAGGATTTCAACGTGGCAGTTAGAATCACGCCTCTTAAATATGCCCAGATTTG
     1200       1210       1220       1230       1240       1250

     1220       1230       1240       1250       1260       1270
  CTATTGGATTAAAGGAAACTACCTGGATTGTAGGGAGGGGTGACACAGTGTTCCCTCCTG
  :::::::::::::::::::::::::::::.::::: :::::::::::::: .: ::  : :: :: 
  CTATTGGATTAAAGGAAACTACCTAGATTGCAGGGAGGGGTGACA-TGCGT--CTTCTTG
     1260       1270       1280       1290       1300       1310

     1280       1290       1300       1310       1320       1330
  GCAGCAATTAAGGGTCTTCATGTTCTTATTTTAGGAGAGGCCAAATTGTTTTTTGTCATT
   :::::  .:.:: :::: .:: .:: ::: :::::::::::     :.: :::::.:::::: 
  CCAGCACCAATGG-TCTTTTTGCACTCATTGTAGGAGAGGC----TAGCTTTTTATCATT
        1320       1330       1340       1350            1360

     1340       1350       1360       1370       1380       1390
  GGCGTGCACACGTGTGTGTGTGTGTGTGTGTAAGGTGTCTTATAATCTTTTACCTA--
  :       ::.: ::::          :::::.:: :      :.:: .:::::::::::::: 
  G------ACTCTTGTG---------GTGTGAGTCA-----CATAGTATCTTTTACCTAGT
        1370                  1380            1390       1400

     1400       1410       1420       1430       1440       1450
  TTTCTTACAATTGCAAGA-TGACTGGCTTTACTATTTGAAAACTGGTTTGTGTATCATAT
  .::::::  ::: :::::.: : : :::::::.:: ::::: ::::::: : ::::   :.: 
  ATTCTTCAAATGGCAAAAATTATTGGCTATATTATTTTAAAACTGTTGTGTG---CGT--
     1410       1420       1430       1440       1450          1460

     1460       1470       1480       1490       1500       1510
  CATATATCATTTAAGCAGTTTGAAGGCATACTTTTGCATAGAAATAAAAAAAAATACTGAT
    :::: :::::::::::: :::::.:::::::::::::::::::: .::::::       :.. 
  --TATAGCATTTAAGCAGTCTGAAAGCATACTTTTGCATAGAGACTTTAAA------GTA
           1470       1480       1490       1500             1510

     1520       1530       1540       1550       1560       1570
  TTGGGGCAATGAGGAATATTTGACAATTAAGTTAATCTTCACGTTTTTGCAAACTT-TGA
  :: ::: :::.::  :::::::::  :::::::::  :::::::: :.: :: :.: 
  TTCGGGTAATAGGGCCTATTTGACAAGGAAGTTAAACTTTCAGTTTTTGGAGAATTCTAA
     1520       1530       1540       1550       1560       1570

     1580       1590       1600       1610       1620       1630
  TTTTTATTTCATCTGAACTTGTTTCAAAGATTTATATTAAATATTTGGCATACAAGAGAT
```

FIG 38 (3 of 7)

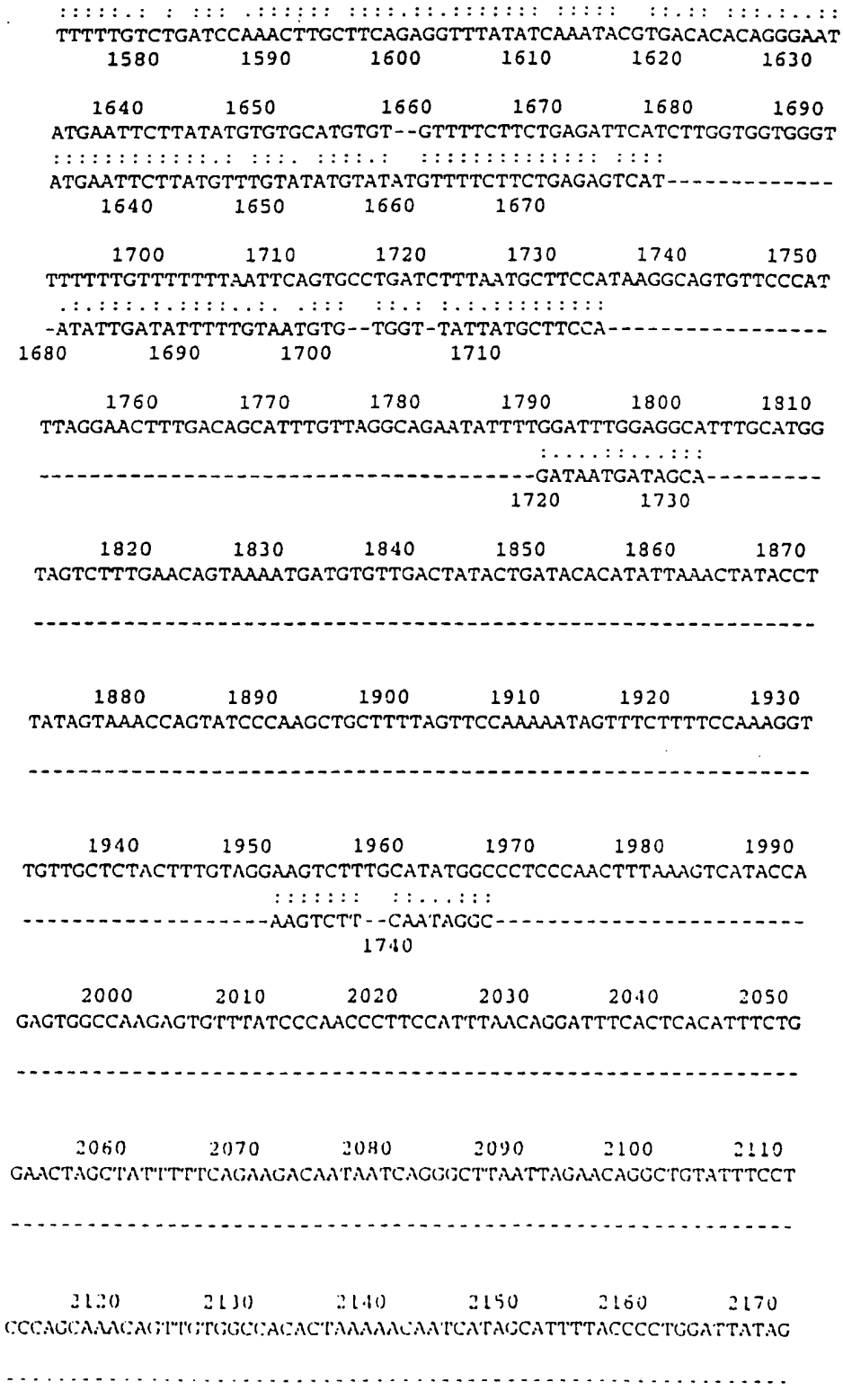

TTTTTGTCTGATCCAAACTTGCTTCAGAGGTTTATATCAAATACGTGACACACAGGGAAT
1580 1590 1600 1610 1620 1630
1640 1650 1660 1670 1680 1690
ATGAATTCTTATATGTGTGCATGTGT--GTTTTCTTCTGAGATTCATCTTGGTGGTGGGT
ATGAATTCTTATGTTTGTATATGTATATGTTTTCTTCTGAGAGTCAT----------
1640 1650 1660 1670
1700 1710 1720 1730 1740 1750
TTTTTTGTTTTTTTAATTCAGTGCCTGATCTTTAATGCTTCCATAAGGCAGTGTTCCCAT
-ATATTGATATTTTTGTAATGTG--TGGT-TATTATGCTTCCA----------
1680 1690 1700 1710
1760 1770 1780 1790 1800 1810
TTAGGAACTTTGACAGCATTTGTTAGGCAGAATATTTTGGATTTGGAGGCATTTGCATGG
----------GATAATGATAGCA---------
1720 1730
1820 1830 1840 1850 1860 1870
TAGTCTTTGAACAGTAAAATGATGTGTTGACTATACTGATACACATATTAAACTATACCT
1880 1890 1900 1910 1920 1930
TATAGTAAACCAGTATCCCAAGCTGCTTTTAGTTCCAAAAATAGTTTCTTTTCCAAAGGT
1940 1950 1960 1970 1980 1990
TGTTGCTCTACTTTGTAGGAAGTCTTTGCATATGGCCCTCCCAACTTTAAAGTCATACCA
----------AAGTCTT--CAATAGGC----------
1740
2000 2010 2020 2030 2040 2050
GAGTGGCCAAGAGTGTTTATCCCAACCCTTCCATTTAACAGGATTTCACTCACATTTCTG
2060 2070 2080 2090 2100 2110
GAACTAGCTATTTTTCAGAAGACAATAATCAGGGCTTAATTAGAACAGGCTGTATTTCCT
2120 2130 2140 2150 2160 2170
CCCAGCAAACAGTTGTGGCCACACTAAAAACAATCATAGCATTTTACCCCTGGATTATAG

FIG 38 (4 OF 7)

```
      2180       2190       2200       2210       2220       2230
CACATCTCATGTTTTATCATTTGGATGGAGTAATTTAAAATGAATTAAATTCCAGAGAAC
                                  :::::::.::::..::..::::
--------------------------------AATTTATAATGTTTTGGATTC--------
                                 1750       1760

      2240       2250       2260       2270       2280       2290
AATGGAAGCATTGCCTGGCAGATGTCACAACAGAATAACCACTTGTTTGGAGCCTGGCAC
     ::.:::::
-----AAACATT-----------------------------------------------------
    1770

      2300       2310       2320       2330       2340       2350
AGTCCTCCAGCCTGATCAAAAATTATTCTGCATAGTTTTCAGTGTGCTTTCTGGGAGCTA
                                :.:.::::. ::
-----------------------------TACGTAGTAGTC--------------------
                              1780

      2360       2370       2380       2390       2400       2410
TGTACTTCTTCAATTTGGAAACTTTTCTCTCTCATTTATAGTGAAAATACTTGGAAGTTA
                                                  :::::.:.. .:
--------------------------------------------------CTTGAAGAGAA
                                                  1790

      2420       2430       2440       2450       2460       2470
CTTTAAGAAAACCAGTGTGGCCTTTTTCCCTCTAGCTTTAAAAGGGCCGCTTTTGCTGGA
:..:::
CAATAA-----------------------------------------------------
1800

      2480       2490       2500       2510       2520       2530
ATGCTCTAGGTTATAGATAAACAATTAGGTATAATAGCAAAAATGAAAATTGGAAGAATG
                                :.:::.:.::.:.:::::.:
-----------------------------TTTATTGGCTATATTGATA------------
                              1810       1820

      2540       2550       2560       2570       2580       2590
CAAAATGGATCAGAATCATGCCTTCCAATAAAGGCCTTTACACATGTTTTATCAATATGA

------------------------------------------------------------

      2600       2610       2620       2630       2640       2650
TTATCAAATCACAGCATATACAGAAAAGACTTGGACTTATTGTATGTTTTTATTTTATGG

------------------------------------------------------------

      2660       2670       2680       2690       2700       2710
CTCTCGGCCTAAGCACTTCTTTCTAAATGTATCGGAGAAAAAAATCAAATGGACTACAAGC

------------------------------------------------------------

      2720       2730       2740       2750       2760       2770
ACGTGTTTGCTGTGCTTGCACCCCAGGTAAACCTGCATTGTAGCAATTTGTAAGGATATT
```

FIG 38 (5 OF 7)

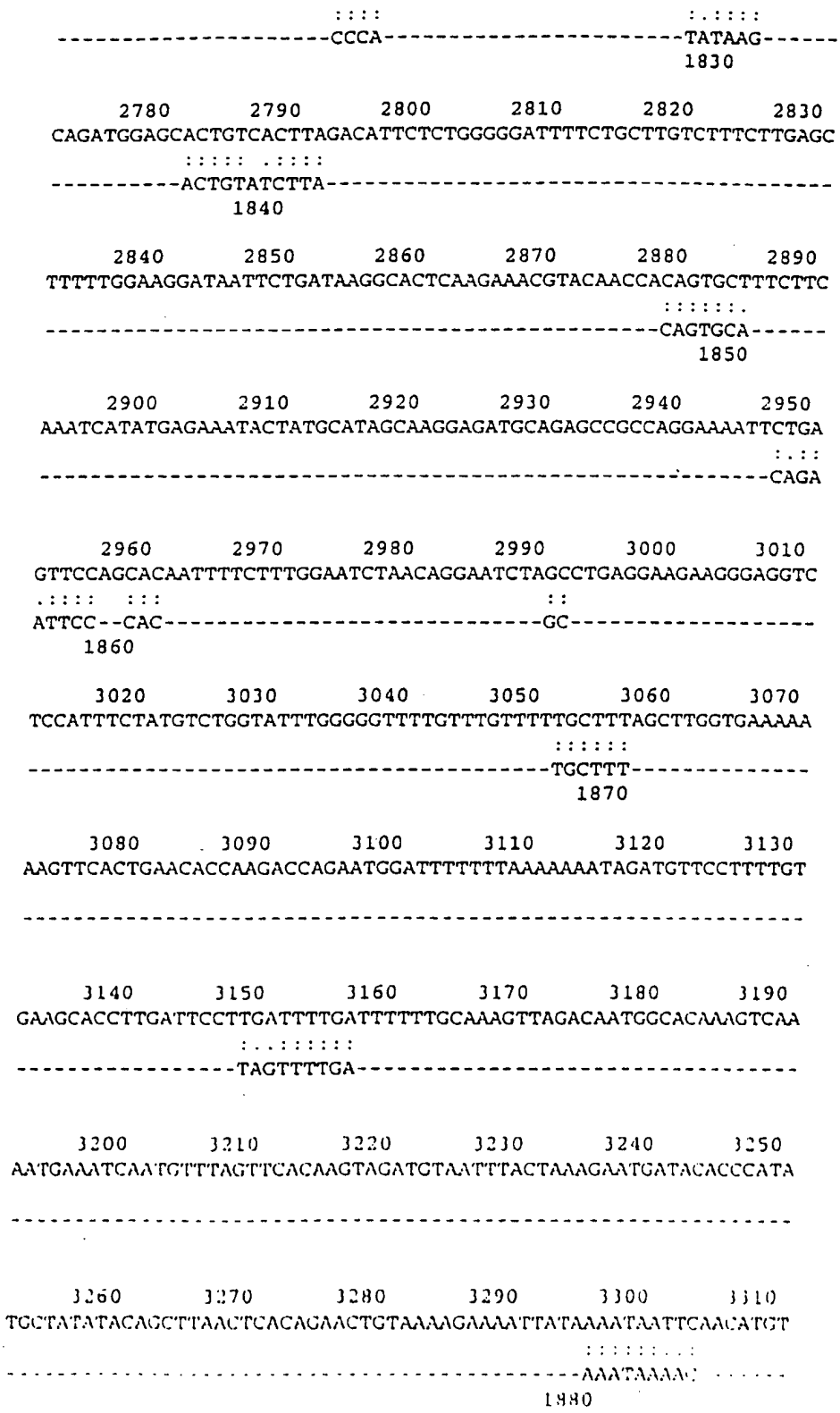

CCCA
TATAAG
1830
2780 2790 2800 2810 2820 2830
CAGATGGAGCACTGTCACTTAGACATTCTCTGGGGGATTTTCTGCTTGTCTTTCTTGAGC
ACTGTATCTTA
1840
2840 2850 2860 2870 2880 2890
TTTTTGGAAGGATAATTCTGATAAGGCACTCAAGAAACGTACAACCACAGTGCTTTCTTC
CAGTGCA
1850
2900 2910 2920 2930 2940 2950
AAATCATATGAGAAATACTATGCATAGCAAGGAGATGCAGAGCCGCCAGGAAAATTCTGA
CAGA
2960 2970 2980 2990 3000 3010
GTTCCAGCACAATTTTCTTTGGAATCTAACAGGAATCTAGCCTGAGGAAGAAGGGAGGTC
ATTCC--CAC
GC
1860
3020 3030 3040 3050 3060 3070
TCCATTTCTATGTCTGGTATTTGGGGGTTTTGTTTGTTTTTGCTTTAGCTTGGTGAAAAA
TGCTTT
1870
3080 3090 3100 3110 3120 3130
AAGTTCACTGAACACCAAGACCAGAATGGATTTTTTTAAAAAAAATAGATGTTCCTTTTGT
3140 3150 3160 3170 3180 3190
GAAGCACCTTGATTCCTTGATTTTGATTTTTTGCAAAGTTAGACAATGGCACAAAGTCAA
TAGTTTTGA
3200 3210 3220 3230 3240 3250
AATGAAATCAATGTTTAGTTCACAAGTAGATGTAATTTACTAAAGAATGATACACCCATA
3260 3270 3280 3290 3300 3310
TGCTATATACAGCTTAACTCACAGAACTGTAAAAGAAAATTATAAAATAATTCAACATGT
AAATAAAAC
1980

FIG 3B (6 OF 7)

```
      3320       3330       3340       3350       3360       3370
CCATCTTTTTAGTGATAATAAAAGAAAGCATGGTATTAAACTATCATAGAAGTAGACAGA

------------------------------------------------------------


      3380       3390       3400       3410       3420       3430
AAAAGAAAAAAGGACTCATGGCATTATTAATATAATTAGTGCTTTACATGTGTTAGTTAT

------------------------------------------------------------


      3440       3450       3460       3470       3480       3490
ACATATTAGAAGCATATTTGCCTAGTAAGGCTAGTAGAACCACATTTCCCAAAGTGTGCT
                                                  ::::::
-------------------------------------------------TTTCCC----------
                                                1890

      3500       3510       3520       3530       3540       3550
CCTTAAACACTCATGCCTTATGATTTTCTACCAAAAGTAAAAAGGGTTGTATTAAGTCAG
                                                  :::::::::.
-------------------------------------------------TTGTAAAAAA----
                                                    1900

      3560       3570       3580       3590       3600       3610
AGGAAGATGCCTCTCCATTTTCCCTCTCTTTATCAGAGGTTCACATGCCTGTCTGCACAT

------------------------------------------------------------


      3620       3630       3640       3650       3660       3670
TAAAAGCTCTGGGAAGACCTGTTGTAAAGGGACAAGTTGAGGTTGTAAAATCTGCATTTA

------------------------------------------------------------


      3680       3690       3700       3710
AATAAACATCTTTGATCACAAAAAAAAAAAAAAAAGGGCGGCCG
                  :::::::::::::::::::::::::
------------------AAAAAAAAAAAAAAAAGGGCGGCCG
                  1910       1920
```

FIG 38 (7 OF 7)

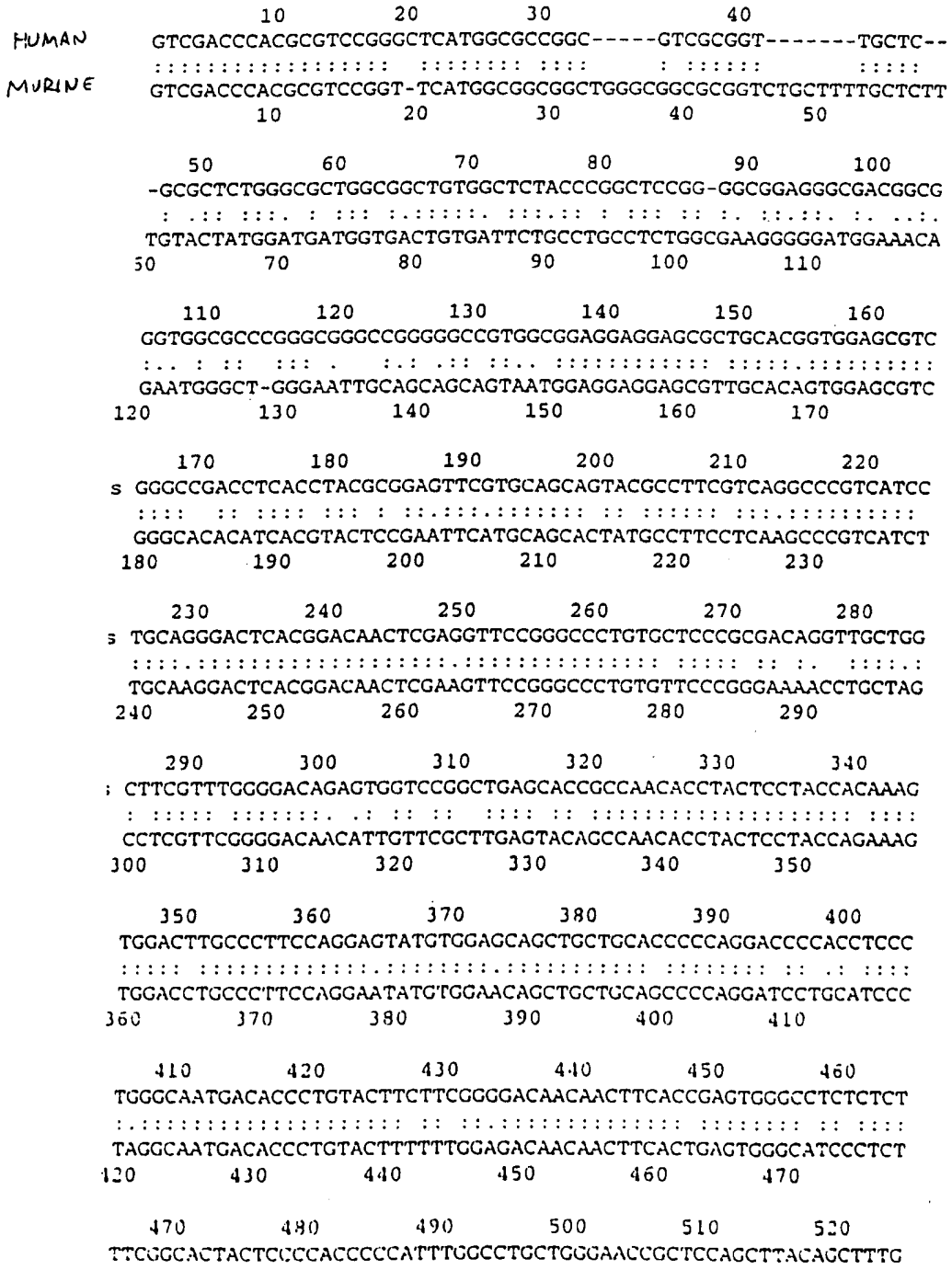


FIG 39 (1 OF 4)

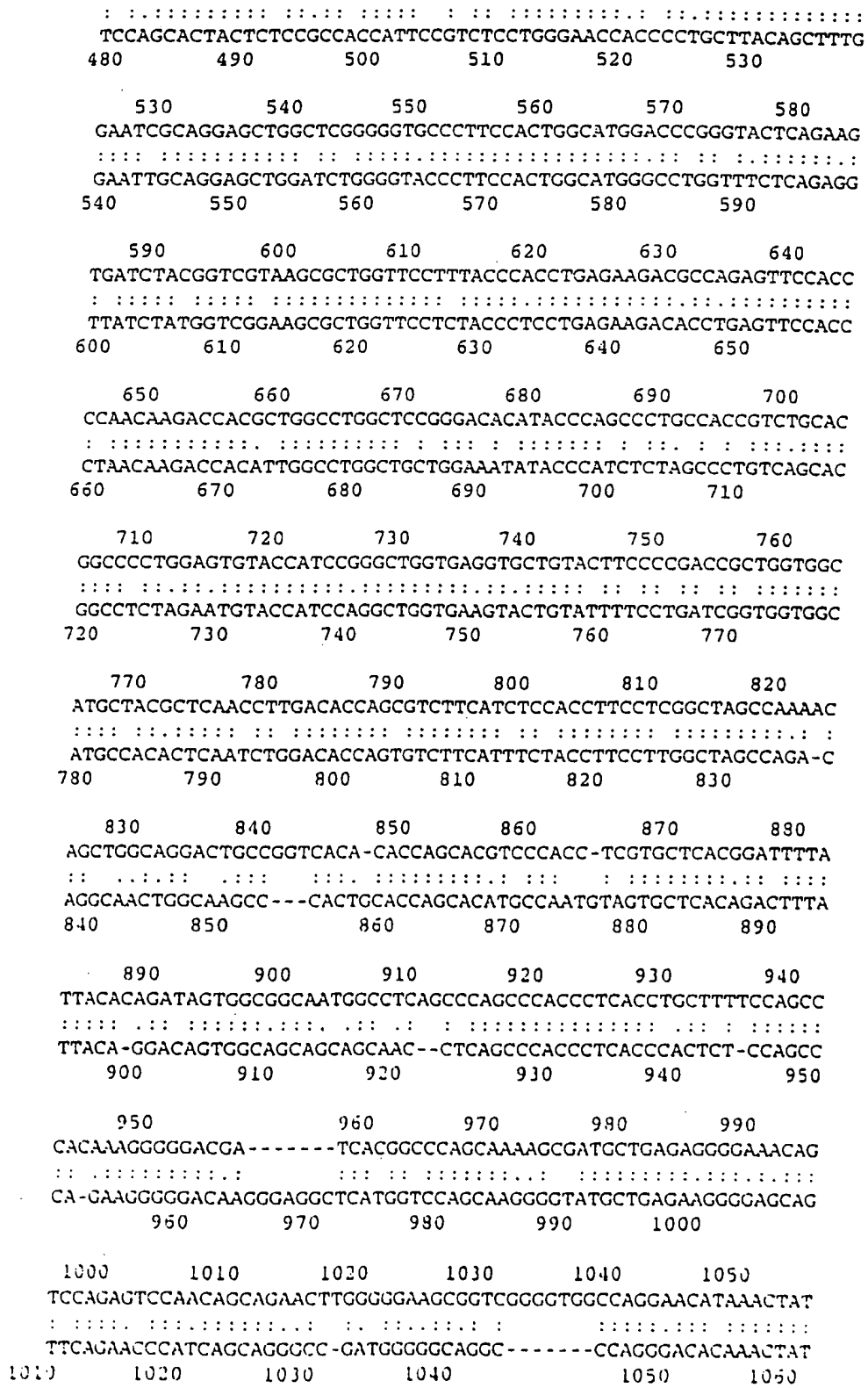


FIG 39 (2 of 4)

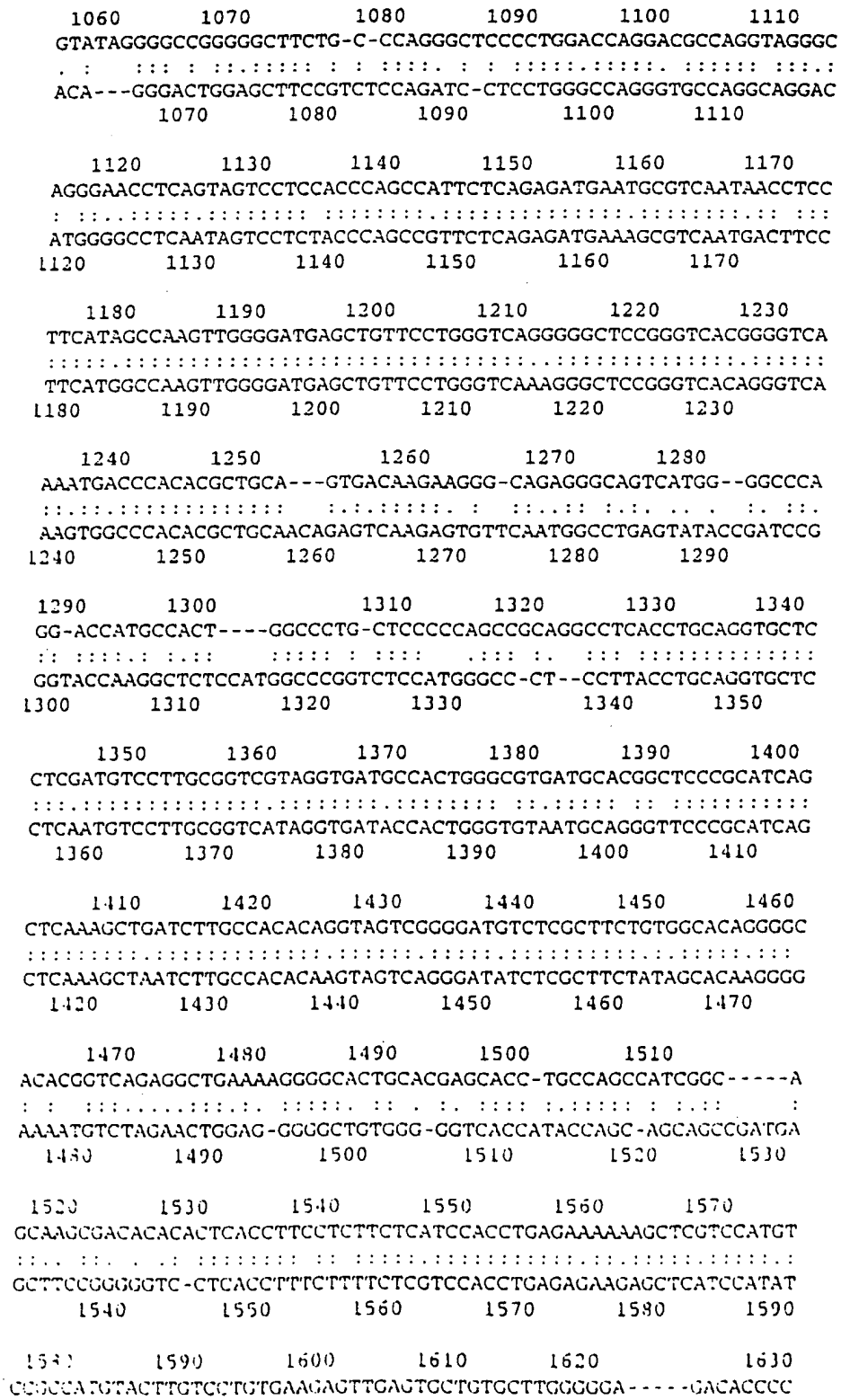


FIG 39 (3 OF 4)

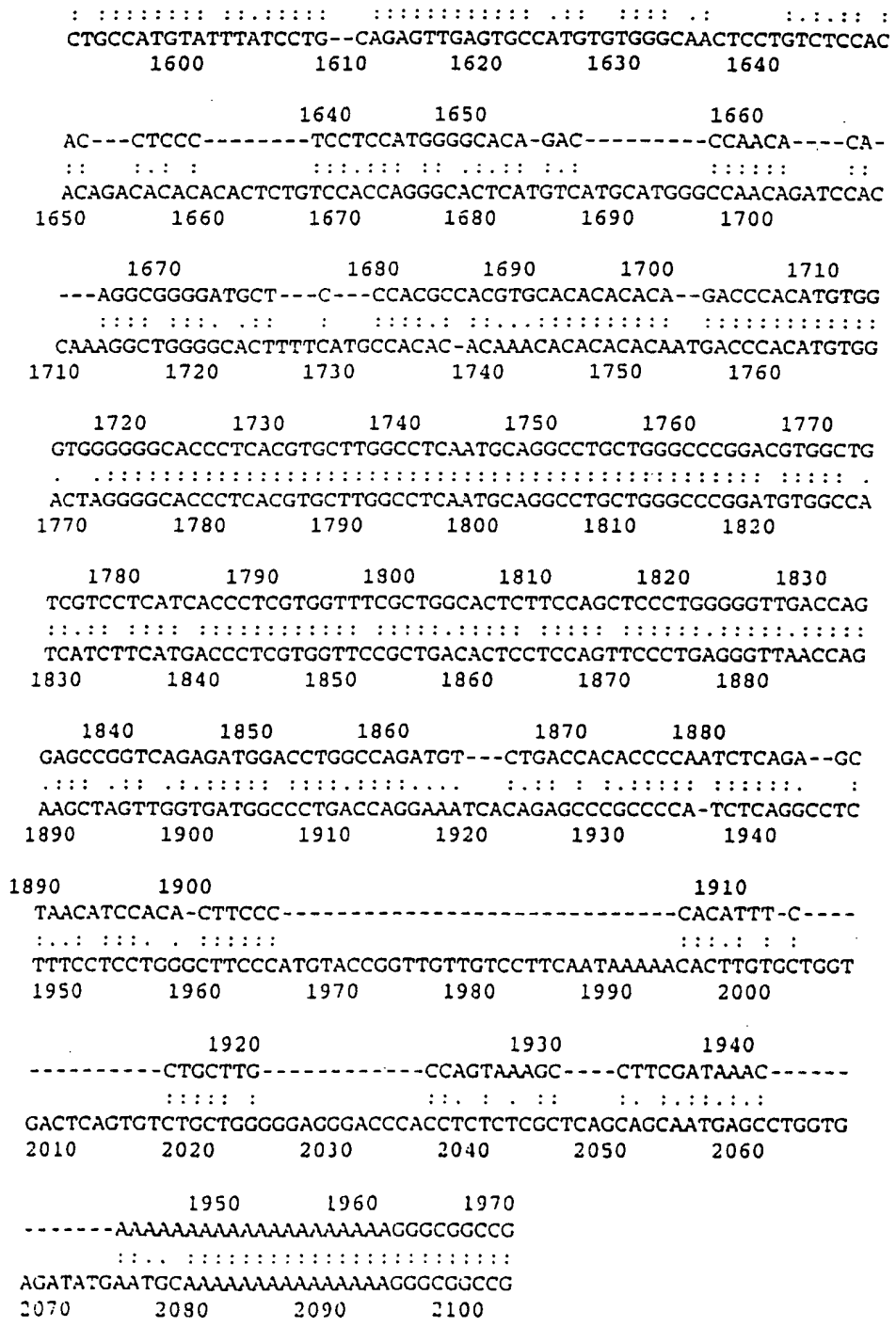


FIG 39 (4 OF 4)

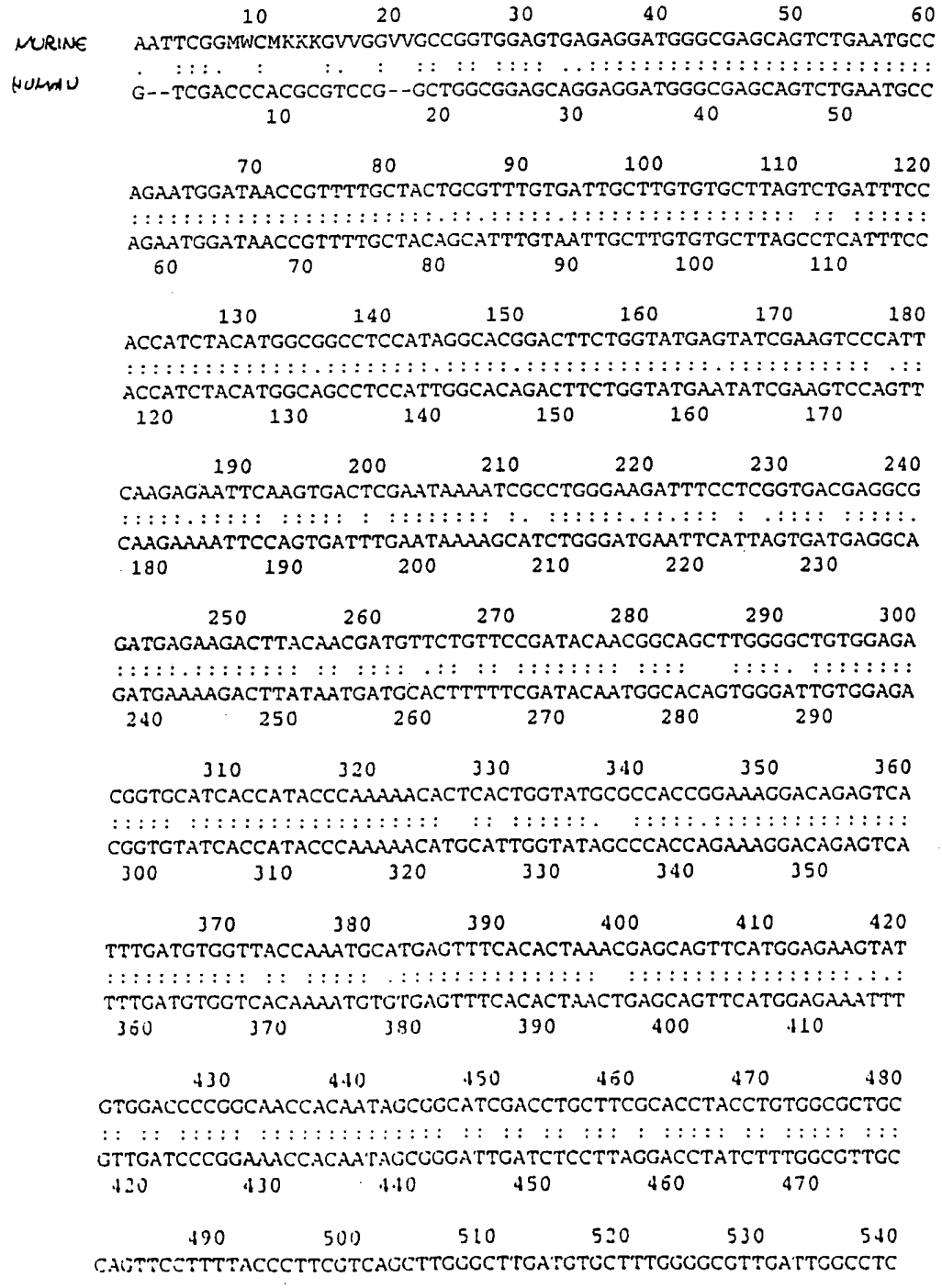

MURINE
HUMAN
10 20 30 40 50 60
AATTCGGMWCMKKKGVVGGVVGCCGGTGGAGTGAGAGGATGGGCGAGCAGTCTGAATGCC
G--TCGACCCACGCGTCCG--GCTGGCGGAGCAGGAGGATGGGCGAGCAGTCTGAATGCC
10 20 30 40 50
70 80 90 100 110 120
AGAATGGATAACCGTTTTGCTACTGCGTTTGTGATTGCTTGTGTGCTTAGTCTGATTTCC
AGAATGGATAACCGTTTTGCTACAGCATTTGTAATTGCTTGTGTGCTTAGCCTCATTTCC
60 70 80 90 100 110
130 140 150 160 170 180
ACCATCTACATGGCGGCCTCCATAGGCACGGACTTCTGGTATGAGTATCGAAGTCCCATT
ACCATCTACATGGCAGCCTCCATTGGCACAGACTTCTGGTATGAATATCGAAGTCCAGTT
120 130 140 150 160 170
190 200 210 220 230 240
CAAGAGAATTCAAGTGACTCGAATAAAATCGCCTGGGAAGATTTCCTCGGTGACGAGGCG
CAAGAAAATTCCAGTGATTTGAATAAAAGCATCTGGGATGAATTCATTAGTGATGAGGCA
180 190 200 210 220 230
250 260 270 280 290 300
GATGAGAAGACTTACAACGATGTTCTGTTCCGATACAACGGCAGCTTGGGGCTGTGGAGA
GATGAAAAGACTTATAATGATGCACTTTTTCGATACAATGGCACAGTGGGATTGTGGAGA
240 250 260 270 280 290
310 320 330 340 350 360
CGGTGCATCACCATACCCAAAAACACTCACTGGTATGCGCCACCGGAAAGGACAGAGTCA
CGGTGTATCACCATACCCAAAAACATGCATTGGTATAGCCCACCAGAAAGGACAGAGTCA
300 310 320 330 340 350
370 380 390 400 410 420
TTTGATGTGGTTACCAAATGCATGAGTTTCACACTAAACGAGCAGTTCATGGAGAAGTAT
TTTGATGTGGTCACAAAATGTGTGAGTTTCACACTAACTGAGCAGTTCATGGAGAAATTT
360 370 380 390 400 410
430 440 450 460 470 480
GTGGACCCCGGCAACCACAATAGCGGCATCGACCTGCTTCGCACCTACCTGTGGCGCTGC
GTTGATCCCGGAAACCACAATAGCGGGATTGATCTCCTTAGGACCTATCTTTGGCGTTGC
420 430 440 450 460 470
490 500 510 520 530 540
CAGTTCCTTTTACCCTTCGTCAGCTTGGGCTTGATGTGCTTTGGGGCGTTGATTGGCCTC

FIG 40 (1 OF 3)

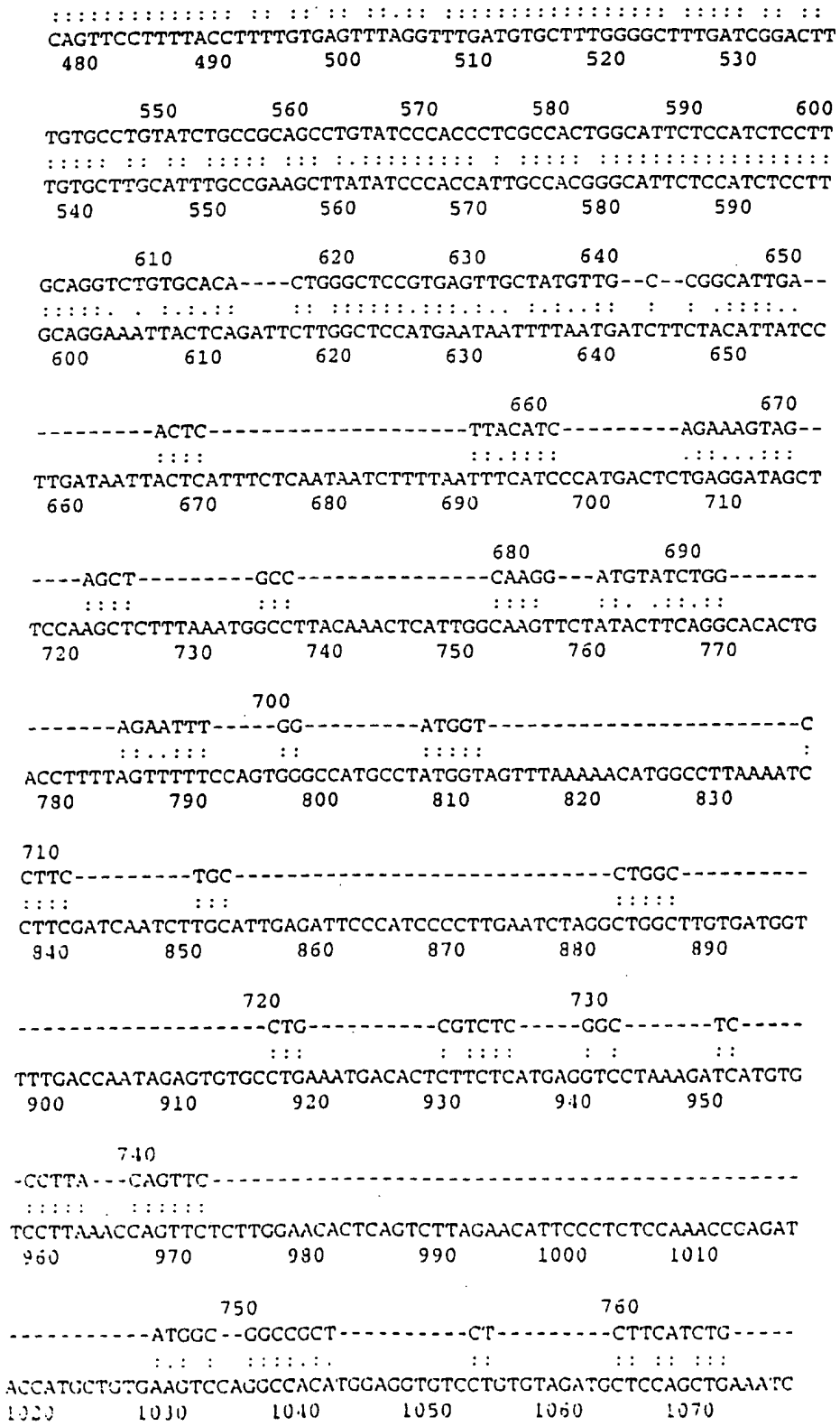


FIG 4C (2 OF 3)

```
                    770               780         790
--------------------GGCTGCCCACA------CCAACCG-GAAAGAGTAC------
                    :.:.::: :::       :::.::. :...:.:..:
CCAAGCTAAGCTCCCAACTGACAGCCAACATCATTTCCAGCCATGTGTGGGAGCCATCCT
1080       1090       1100       1110       1120       1130

            800                 810
---------ACCTTAA---------TGAAGGCTT--------------ATC---------
          .:::::::          .:::.:::            :::
GGATGTCCAGCCTTAACAAGCCTTCAGAGGACTTCAGCCACAGCTATTATCTTACTACAT
1140       1150       1160       1170       1180       1190

       820                 830                          840
----GTGTGGC----ATGAAGGG-----AGGCTG-----------CCTG-----CT----
    :::.:.:    ::.:::..     ..:::::           :::.      ::
CCTTGTGAGACTCTAATAAAGAACCAACTAGCTGAGCCCAATCAACCTATGGAACTGATA
1200       1210       1220       1230       1240       1250

            850              860        870
------TAATGATTAATATTTTT------CATACATTTTTTT------------------
      .::::::.:.:. ::::       :..: :.......
GAAATAAAATGAATTGTTGTTTTGTGCCGCTAAAAAAAAAAAAAAAAAAAAAAAAAAAAG
1260       1270       1280       1290       1300       1310


---------

GGCGGCCGC
1320
```

FIG 40 (3 of 3)

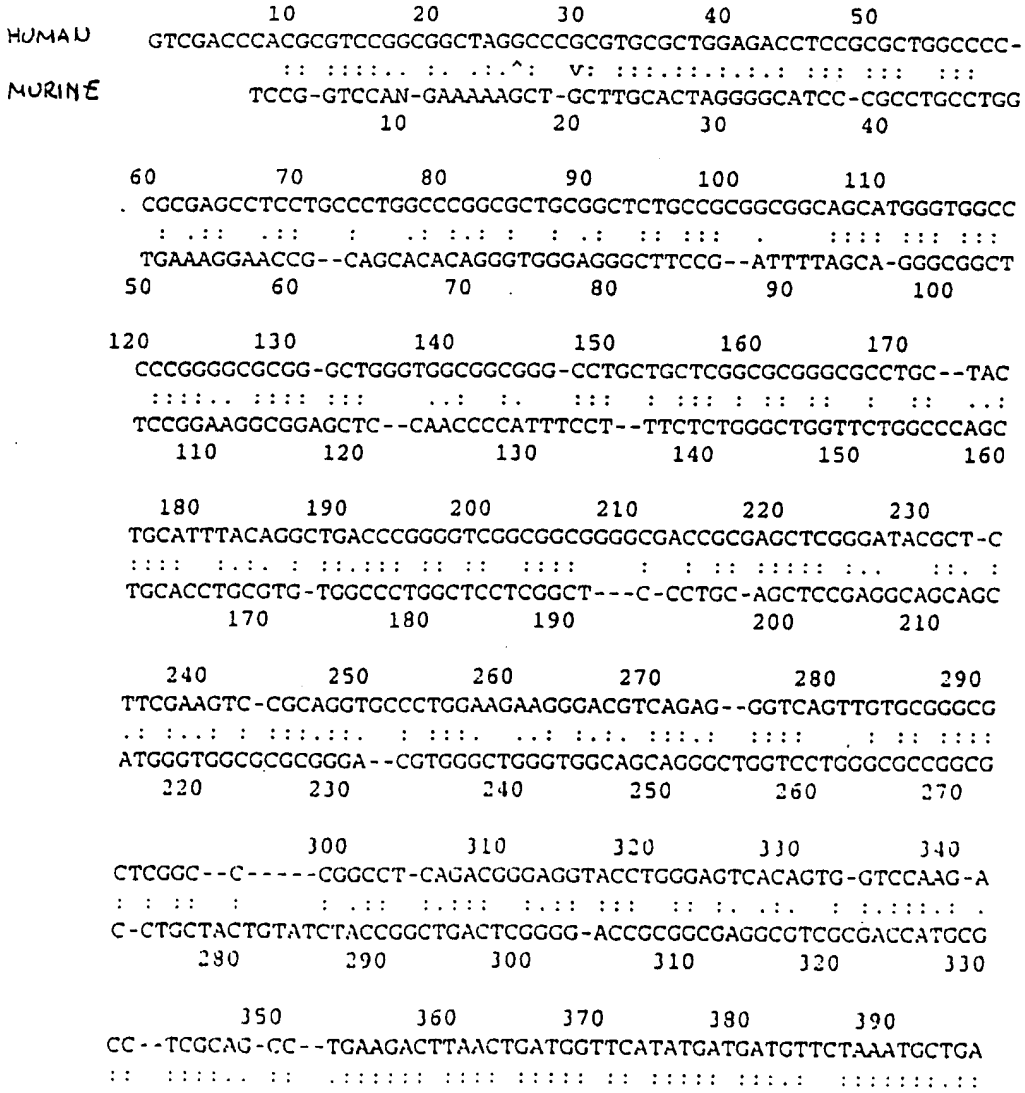


FIG 41 (1 OF 2)

```
   CCCTTCGCGATCCGCAGAAGACCTAACCGATGGCTCCTATGACGATATCTTAAATGCAGA
          340        350        360        370        380        390

    400        410        420        430        440        450
. ACAACTTCAGAAACTCCTTTACCTGCTGGAGTCAACGGAGGATCCTGTAATTATTGAAAG
  .::.::: ::::::: :: :: :::::::::::::: :: :::::::: :::: :::::.
  GCAGCTTAAGAAACTTCTGTATCTGCTGGAGTCAACCGACGATCCTGTCATTACTGAAAA
          400        410        420        430        440        450

    460        470        480        490        500        510
. AGCTTTGATTACTTTGGGTAACAATGCAGCCTTTTCAGTTAACCAAGCTATTATTCGTGA
  .:: :::.: :: ::::::.:: :::::::::::: :: . ::::::.:: ::::::::::
  GGCCTTGGTCACCTTGGGAAATAATGCAGCCTTCTCCACTAACCAGGCCATTATTCGTGA
          460        470        480        490        500        510

    520        530        540        550          560        570
  ATTGGGTGGTATTCCAATTGTTGCAAACAAAATCAACCATTCC--AACCAGAGTATTAAA
  .:::::::::::: :::::::::: ::::::::::::::  : ::  :::::.:::::::::
  GTTGGGTGGTATCCCAATTGTTGGAAACAAAATCAAC--TCCCTGAACCAAAGTATTAAA
          520        530        540          550        560

     580        590        600        610        620        630
  GAGAAAGCTTTAAATGCACTAAATAACCTGAGTGTGAATGTTGAAAATCAAATCAAGATA
  :::::::::::::::::::::.:::::::::::::::::::::::::::::::::  ::::::
  GAGAAAGCTTTAAATGCACTGAATAACCTGAGTGTGAATGTTGAAAATCAAACTAAGATA
570        580        590        600        610        620

    640        650        660        670        680        690
  AAGATATACATCAGTCAAGTATGTGAGGATGTCTTCTCTGGTCCTCTGAACTCTGCTGTG
  ::::::::::.::  :::::: :::::::: :::::  ::X.
  AAGATATACGTCCCTCAAGTCTGTGAGGACGTCTTTGCTGAC
630        640        650        660        670

    700        710        720        730        740        750
  CAGCTGGCTGGACTGACATTGTTGACAAACATGACTGTTACCAATGACCACCAGCACATG
```

FIG 41 (2 OF 2)

```
T182.hum.pep  MNMTQARVLVAAVVGLVAVLLYASIHKIEEGHLAVYYRGGALLTSPSGPGYHIMLPFITTFRSVQT
T182.mus.pep  MNMTQARLLVAAVVGLVAILLYASIHKIEEGHLAVYYRGGALLTSPSGPGYHIMLPFITTFRSVQT
T181.hum.pep    MAQLGAVVAVASSFFCASLFSAVHKIEEGHIGVYYRGGALLTSTSGPGFHLMLPFITSYKSVQT
T181.mus.pep    MAQLGAVVAVASSFFCASLFSAVHKIEEGHIGVYYRGGALLTSTSGPGFHLMLPFITSYKSVQT

T182.hum.pep  TLQTDEVKNVPCGTSGGVMIYIDRIEVVNMLAPYAVFDIVRNYTADYDKTLIFNKIHHELNQFCSA
T182.mus.pep  TLQTDEVKNVPCGTSGGVMIYIDRIEVVNMLAPYAVFDIVRNYTADYDKTLIFNKIHHELNQFCSA
T181.hum.pep  TLQTDEVKNVPCGTSGGVMIYFDRIEVVNFLVPNAVYDIVKNYTADYDKALIFNKIHHELNQFCSV
T181.mus.pep  TLQTDEVKNVPCGTSGGVMIYFDRIEVVNFLVPNAVYDIVKNYTADYDKALIFNKIHHELNQFCSV

T182.hum.pep  HTLQEVYIELFDQIDENLKQALQKDLNLMAPGLTIQAVRVTKPKIPEAIRRNFELMEAEKTKLLIA
T182.mus.pep  HTLQEVYIELFDQIDENLKQALQKDLNTMAPGLTIQAVRVTKPKIPEAIRRNFELMEAEKTKLLIA
T181.hum.pep  HTLQEVYIELFDQIDENLKLALQQDLTSMAPGLVIQAVRVTKPNIPEAIRRNYELMESEKTKLLIA
T181.mus.pep  HTLQEVYIELFDQIDENLKLALQQDLTSMAPGLVIQAVRVTKPNIPEAIRRNYELMESEKTKLLIA

T182.hum.pep  KQKQKVVEKEAETERKKAVIEAEKIAQVAKIRFQQKVMEKETEKRISEIEDAAFLAREKAKADAEY
T182.mus.pep  AQKQKVVEKEAETERKRAVIEAEKIAQVAKIRFQQKVMEKETEKRISEIEDAAFLAREKAKADAEY
T181.hum.pep  AQKQKVVEKEAETERKKALIEAEKVAQVAEITYGQKVMEKETEKKISEIEDAAFLAREKAKADAEC
T181.mus.pep  AQKQKVVEKEAETERKKALIEAEKVAQVAEITYGQKVMEKETEK...

T182.hum.pep  YAAHKYATSNKHKLTPEYLELKKYQAIASNSKIYFGSNIPNMFVDSSCALKYSDIRTGRESSLPSK
T182.mus.pep  YAAHKYATSNKHKLTPEYLELKKYQAIASNSKIYFGSNIPSMFVDSSCALKYSDGRTGREDSLPPE
T181.hum.pep  YTAMKIAEANKLKLTPEYLQLMKYKAIASNSKIYFGKDIPNMFMDSAGSV------SKQFEGLADK
C42C1.a       YKAQKQADSNKILLTKEYLELQKIRAIASNNKIYYGDSIPQAFV--MGTTQQTV

T182.hum.pep  EALEPSGENVIQ--NKESTG
T182.mus.pep  EAREPSGESPIQ--NKENAG
T181.hum.pep  LSFGLE-DEPLETATKEN
```

FIG. 42

```
                10        20        30        40        50        60
inputs MATLWGGLLRLGSLLSLSCLALSVLLLAQLSDAAKNFEDVRCKCICPPYKENSGHIYNKN
       :      :: : ...  .::       :.. ..:.:. ::.:::::::::.. :::::::.:
       MK-----LLSLVAVV--GCL------LVPPAEANKSSEDIRCKCICPPYRNISGHIYNQN
                    10                  20        30        40

                70        80        90        100       110       120
inputs ISQKDCDCLHVVEPMPVRGPDVEAYCLRCECKYEERSSVTIKVTIIIYLSILGLLLLYMV
       .:::::.:::::::::: : ::::::: :::.::::::.::::.:::::..: ::::::.
       VSQKDCNCLHVVEPMPVPGHDVEAYCLLCECRYEERSTTTIKVIIVIYLSVVGALLLYMA
        50        60        70        80        90        100

               130       140       150       160       170       180
inputs YLTLVEPILKRRLFGHAQLIQSDDDIGDHQPFANAHDVLARSRSRANVLNKVEYAQQRWK
       .: ::.: : :.  . .. ......  : .. :.: . :. .:. ..::..:: ::::::
       FLMLVDP-LIRKPDAYTEQLHNEEENEDARSMAAAAASLGGPRA-NTVLERVEGAQQRWK
       110       120       130       140       150       160

              190
inputs LQVQEQRKSVFDRHVVLSN
       :::::::::::::: .:::
       LQVQEQRKTVFDRHKMLSN
         170       180
```

FIG. 43

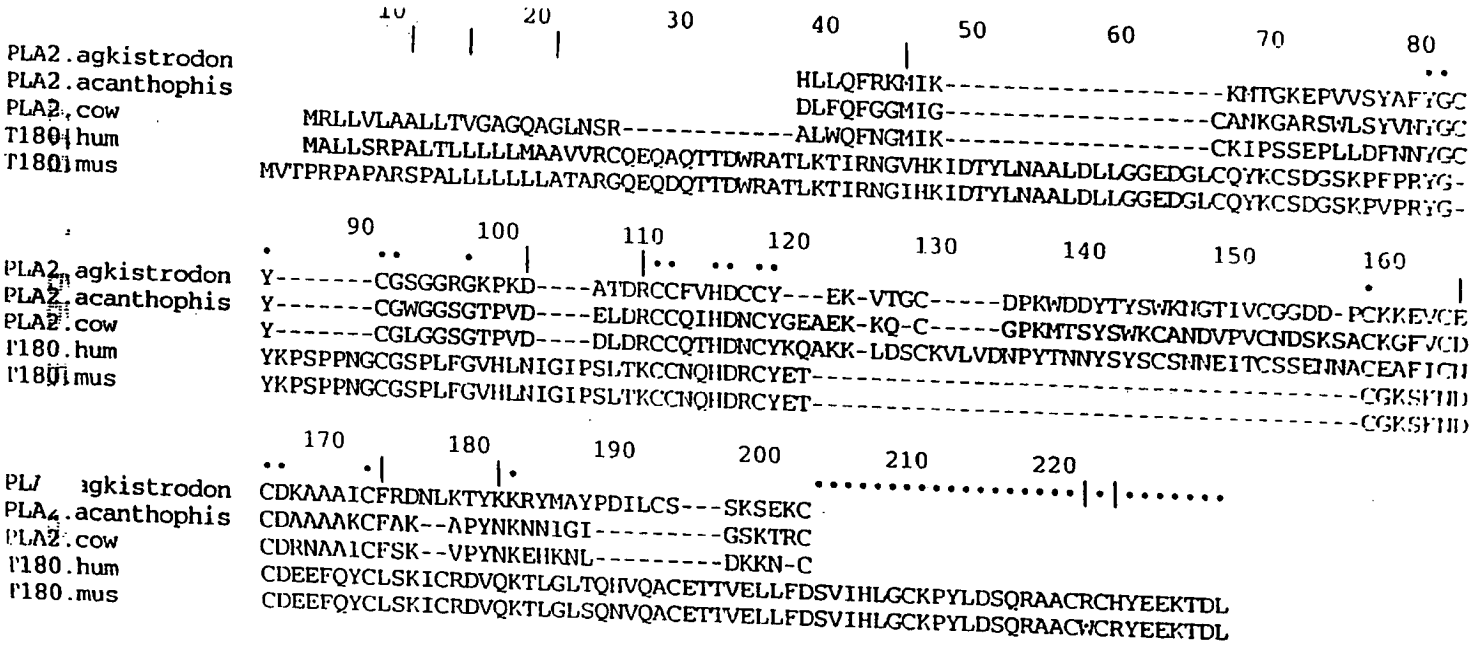
```
                10         20         30         40         50         60
inputs MASLWCGNLLRLGSGLSMSCLALSVLLLAQLTGAAKNFEDVRCKCICPPYKENPGHIYNK
       :      .:: : . .  .::       :.. . :.:. ::.:::::::::.. .::::::.
       M------KLLCLVAVV--GCL------LVPPAQANKSSEDIRCKCICPPYRNISGHIYNQ
                      10                  20         30         40

                70         80         90        100        110        120
inputs NISQKDCDCLHVVEPMPVRGPDVEAYCLRCECKYEERSSVTIKVTIIIYLSILGLLLLYM
       :.::::::.:::::::::: : ::::::: :::.::::::.::::.:.::::::.: :::::
       NVSQKDCNCLHVVEPMPVPGHDVEAYCLLCECRYEERSTTTIKVIIVIYLSVVGALLLYM
         50         60         70         80         90        100

              130        140        150        160        170        180
inputs VYLTLVEPILKRRLFGHSQLLQSDDDVGDHQPFANAHDVLARSRSRANVLNKVEYAQQRW
       ..: ::.: : :.  . .. :.....  : .  :.: . .. .:. ..::..:: :::::
       AFLMLVDP-LIRKPDAYTEQLHNEEENEDARTMATAAAASIGGPRA-NTVLERVEGAQQRW
        110        120        130        140        150        160

             190        200
inputs KLQVQEQRKSVFDRHVVLSN
       ::::::::::.::::: .:::
       KLQVQEQRKTVFDRHKMLSN
         170        180
```

FIG. 44


10 20 30 40 50 60 70 80
PLA2.agkistrodon
PLA2.acanthophis
PLA2.cow
T180.hum
T180.mus
HLLQFRKMIK----------KMTGKEPVVSYAFYGC
DLFQFGGMIG----------CANKGARSWLSYVNYGC
MRLLVLAALLTVGAGQAGLNSR----------ALWQFNGMIK----------CKIPSSEPLLDFNNYGC
MALLSRPALTLLLLLMAAVVRCQEQAQTTDWRATLKTIRNGVHKIDTYLNAALDLLGGEDGLCQYKCSDGSKPFPRYG-
MVTPRPAPARSPALLLLLLATARGQEQDQTTDWRATLKTIRNGIHKIDTYLNAALDLLGGEDGLCQYKCSDGSKPVPRYG-
90 100 110 120 130 140 150 160
PLA2.agkistrodon
PLA2.acanthophis
PLA2.cow
T180.hum
T180.mus
Y-------CGSGGRGKPKD----ATDRCCFVHDCCY---EK-VTGC-----DPKWDDYTYSWKNGTIVCGGDD-PCKKEVCE
Y-------CGWGGSGTPVD----ELDRCCQIHDNCYGEAEK-KQ-C-----GPKMTSYSWKCANDVPVCNDSKSACKGFVCD
Y-------CGLGGSGTPVD----DLDRCCQTHDNCYKQAKK-LDSCKVLVDNPYTNNYSYSCSNNEITCSSENNACEAFICN
YKPSPPNGCGSPLFGVHLNIGIPSLTKCCNQHDRCYET----------CGKSFNV
YKPSPPNGCGSPLFGVHLNIGIPSLTKCCNQHDRCYET----------CGKSFNV
170 180 190 200 210 220
PLA2.agkistrodon
PLA2.acanthophis
PLA2.cow
T180.hum
T180.mus
CDKAAAICFRDNLKTYKKRYMAYPDILCS---SKSEKC
CDAAAAKCFAK--APYNKNNIGI---------GSKTRC
CDRNAAICFSK--VPYNKEHKNL---------DKKN-C
CDEEFQYCLSKICRDVQKTLGLTQHVQACETTVELLFDSVIHLGCKPYLDSQRAACRCHYEEKTDL
CDEEFQYCLSKICRDVQKTLGLSQNVQACETTVELLFDSVIHLGCKPYLDSQRAACWCRYEEKTDL

Input file T187human1; Output File T187human1.pat
Sequence length 2490

```
CCACGCGTCCGGCCAGGGGCGGGAGGGAGGAATGGTTGCTTCACGCCCCGGGGGAAGAGACGGGAAGCTCGGCTCTGGG  79

TTGCGGGCCCCGGCGTCTCCGCGTGGGGCGCACCGTCCGACCCGCCCCTCCCGGTGTGCAGCGCCCCGCACCGCCCCGC  158

CTCGCCTGGGAGAAGCCGCCGGGACGCGCCGGGCTGGAGTGGGCGGTTATAGGCTTTGAGCTAGGCCGTTTCCGGGAGG  237

CGGAGCTCAGACCCCATTTCCTTTCTCCACATCCAGGTCAGGTGGCGTTTGCTGTGGCGGCTAGGCCCGCGTGCGCTGG  316

                                                                    M  G      2
AGACCTCCGCGCTGGCCCCCGCGAGCCTCCTGCCCTGGCCCGGCGCTGCGGCTCTGCCGCGGCGGCAGC ATG GGT    391

 G  P  R  G  A  G  W  V  A  A  G  L  L  L  G  A  G  A  C  Y    22
GGC CCC CGG GGC GCG GGC TGG GTG GCG GCG GGC CTG CTG CTC GGC GCG GGC GCC TGC TAC  451

 C  I  Y  R  L  T  R  G  R  R  R  G  D  R  E  L  G  I  R  S    42
TGC ATT TAC AGG CTG ACC CGG GGT CGG CGG CGG GGC GAC CGC GAG CTC GGG ATA CGC TCT  511

 S  K  S  A  G  A  L  E  E  G  T  S  E  G  Q  L  C  G  R  S    62
TCG AAG TCC GCA GGT GCC CTG GAA GAA GGG ACG TCA GAG GGT CAN TTG TGC GGG CGC TCG  571

 A  R  P  Q  T  G  G  T  W  E  S  Q  W  S  K  T  S  x  P  E    82
GCC CGG CCT CAG ACN GGA GGT ACC TGG GAG TCA CAG TGG TCC AAG ACC TCG CAN CCT GAA  631

 D  L  T  D  G  S  Y  D  D  V  L  N  A  E  Q  L  Q  K  L  L   102
GAC TTA ACT GAT GGT TCA TAT GAT GAT GTT CTA AAT GCT GAA CAA CTT CAG AAA CTC CTT  691

 Y  L  L  E  S  T  E  D  P  V  I  I  E  R  A  L  I  T  L  G   122
TAC CTG CTG GAG TCA ACG GAG GAT CCT GTA ATT ATT GAA AGA GCT TTG ATT ACT TTG GGT  751

 N  N  A  A  F  S  V  N  Q  A  I  I  R  E  L  G  G  I  P  I   142
AAC AAT GCA GCC TTT TCA GTT AAC CAA GCT ATT ATT CGT GAA TTG GGT GGT ATT CCA ATT  811

 V  A  N  K  I  N  H  S  N  Q  S  I  K  E  K  A  L  N  A  L   162
GTT GCA AAC AAA ATC AAC CAT TCC AAC CAG AGT ATT AAA GAG AAA GCT TTA AAT GCA CTA  871

 N  N  L  S  V  N  V  E  N  Q  I  K  I  K  V  Q  V  L  K  L   182
AAT AAC CTG AGT GTG AAT GTT GAA AAT CAA ATC AAG ATA AAG GTG CAA GTT TTG AAA CTG  931

 L  L  N  L  S  E  N  P  A  M  T  E  G  L  L  R  A  Q  V  D   202
CTT TTG AAT TTG NCT GAA AAT CCA GCC ATG ACA GAA GGA CTT CTC CGT GCC CAA GTG GAT  991

 S  S  F  L  S  L  Y  D  S  H  V  A  K  E  I  L  L  R  V  L   222
TCA TCA TTC CTT TYC CTT TAT GAC AGC CAC GTA GCA AAG GAG ATT CTT CTT CGA GTA CTT 1051

 T  L  F  Q  N  I  K  N  C  L  K  I  E  G  H  L  A  V  Q  P   242
ACG CTA TTT CAG AAT ATA AAG AAC TGC CTC AAA ATA GAA GGC CAT TTA GCT GTG CAG CCT 1111

 T  F  T  E  G  S  L  F  F  L  L  H  G  E  E  C  A  Q  K  I   262
ACT TTC ACT GAA GGT TCA TTG TTT TTC CTG TTA CAT GGA GAA GAA TGT GCC CAG AAA ATA 1171

 R  A  L  V  D  H  H  D  A  E  V  K  E  K  V  V  T  I  I  P   282
AGA GCT TTA GTT GAT CAC CAT GAT GCA GAG GTG AAG GAA AAG GTT GTA ACA ATA ATA CCC 1231

 K  I  *                                                        285
AAA ATC TGA                                                    1240

TTGGTCATATTTTTCCAAAGAGTAATGCAGTCTGGATATAAATGTATTTTCTGTCTTCCTTATAAGGGGATTCTCCCAG  1319

CTGCTAAATTTAAACAGTAAATATCACATTTTGTCATTAACACAGCTATAACTTGCCGTGGTTCTCAGATTTATTTTGG  1398

ACTATTTTGATGCCAAGTGAATATAAGAGCTTGTACTGAAACCATTTATTTCTTTCTATTTTGCTATTTGCAAATGCTT  1477

GTTATCTTCCCTACATGAAGTGGCAGTAACCTTTTTCACATTTAAGCTACCCTTCTACCTTTTGAAGTGATTTGCAGTT  1556

ACTCATCTGAGACAGCATCAGTATTTGACTAAATCATTGTTTCACAACTGAATAGTCTTGTTCTTTTAGTAGCAATGAA  1635

ATCCTAAGCTCTTGAGGCCATTCACCTGCCAACCTGACCATACTGCTTTCAAAAGTCTTTTCTCATCAGTAGAATCTAT  1714
```

FIG 4C (1 of 2)

TTTGGTCACTTCTAGTCAATGAAAAATGTAAACTTTTAGGAGAGAATGTTTCCTAGGACTCACCCACTCCATTCAATGT 1793

TACATATAAAATAGTGTGATCAATCACAATGTCCATCTTTAGACAGTTGGTTAAATAAATTATCTGGTCTTTGAAAAGA 1872

CCGTGCTGGGCGCGGTGGCTCTTGCCTGTAATCCCAGCACTTTGGGAGGCTGAGGCGGGCAGATCACCTGAGATCGGGA 1951

GTTTGAGACCAAGCCTGACCAATATGGAGAAACCCTGTCTCTACTAAGAATACAAAATTAGCTGGGCATGGTGGTGCAT 2030

GCCTGTAATCCCAGCTACTTGGGAGGCCGAGGCAGGAGAATTGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGGTGAG 2109

ATAGCGCCATTGCACTCCAGCCTGGGCAACAAGAGCAAAACTCTGTCTCAAAAAAAAAAAAAAAATGATGGAGCTCCGAA 2188

TGTGCTTAAGTGGAAAGATATCTATGAAATATGGTGGTTTTTTAAAACACAAAAATTATAGAATATGGGATCCCGTGTG 2267

TGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTTTGAATGAAAAATGCTTATGTATTGACAGAACACTT 2346

CTAGAATGATACCCAAACTCCTGGAGTGGGAGTGGGGAATGCCTTCTACGTACACACTGTTCTACTGTTTGAATTTTTT 2425

AATATGAGCCCAAATTGTATAATCTTTTTTTAATAAAGGGGAGAAAAATCAAAAAAAAAAAAAAA 2490

FIG 4G (2 of 2)

```
Cotaninput file T187human23; Output File T187human23.pat
Sequence length 2595

CCACGCGTCCGGCCAGGGGCGGGAGGGAGGAATGGTTGCTTCACGCCCCGGGGGAAGAGACGGGAAGCTCGGCTCTGGG  79

TTGCGGGCCCCGGCGTCTCCGCGTGGGGCGCACCGTCCGACCCGCCCCTCCCGGTGTGCAGCGCCCCGCACCGCCCCGC  158

CTCGCCTGGGAGAAGCCGCCGGGACGCGCCGGGCTGGAGTGGGCGGTTATAGGCTTTGAGCTAGGCCGTTTCCGGGAGG  237

CGGAGCTCAGACCCCATTTCCTTTCTCCACATCCAGGTCAGGTGGCGTTTGCTGTGGCGGCTAGGCCCGCGTGCGCTGG  316

                                                                    M  G      2
AGACCTCCGCGCTGGCCCCCGCGAGCCTCCTGCCCTGGCCCGGCGCTGCGGCTCTGCCGCGGCGGCAGC ATG GGT   391

 G  P  R  G  A  G  W  V  A  A  G  L  L  L  G  A  G  A  C  Y                    22
GGC CCC CGG GGC GCG GGC TGG GTG GCG GCG GGC CTG CTG CTC GGC GCG GGC GCC TGC TAC  451

 C  I  Y  R  L  T  R  G  R  R  R  G  D  R  E  L  G  I  R  S                    42
TGC ATT TAC AGG CTG ACC CGG GGT CGG CGG CGG GGC GAC CGC GAG CTC GGG ATA CGC TCT  511

 S  K  S  A  E  D  L  T  D  G  S  Y  D  D  V  L  N  A  E  Q                    62
TCG AAG TCC GCA GAA GAC TTA ACT GAT GGT TCA TAT GAT GAT GTT CTA AAT GCT GAA CAA  571

 L  Q  K  L  L  Y  L  L  E  S  T  E  D  P  V  I  I  E  R  A                    82
CTT CAG AAA CTC CTT TAC CTG CTG GAG TCA ACG GAG GAT CCT GTA ATT ATT GAA AGA GCT  631

 L  I  T  L  G  N  N  A  A  F  S  V  N  Q  I  P  M  K  L  V                   102
TTG ATT ACT TTG GGT AAC AAT GCA GCC TTT TCA GTT AAC CAA ATC CCT ATG AAG TTG GTC  691

 T  G  I  T  F  A  I  I  R  E  L  G  G  I  P  I  V  A  N  K                   122
ACT GGC ATC ACA TTC GCT ATT ATT CGT GAA TTG GGT GGT ATT CCA ATT GTT GCA AAC AAA  751

 I  N  H  S  N  Q  S  I  K  E  K  A  L  N  A  L  N  N  L  S                   142
ATC AAC CAT TCC AAC CAG AGT ATT AAA GAG AAA GCT TTA AAT GCA CTA AAT AAC CTG AGT  811

 V  N  V  E  N  Q  I  K  I  K  I  Y  I  S  Q  V  C  E  D  V                   162
GTG AAT GTT GAA AAT CAA ATC AAG ATA AAG ATA TAC ATC AGT CAA GTA TGT GAG GAT GTC  871

 F  S  G  P  L  N  S  A  V  Q  L  A  G  L  T  L  L  T  N  M                   182
TTC TCT GGT CCT CTG AAC TCT GCT GTG CAG CTG GCT GGA CTG ACA TTG TTG ACA AAC ATG  931

 T  V  T  N  D  H  Q  H  M  L  H  S  Y  I  T  D  L  F  Q  V                   202
ACT GTT ACC AAT GAC CAC CAG CAC ATG CTT CAC AGT TAC ATT ACA GAC CTG TTC CAG GTG  991


 L  L  T  G  N  G  N  T  K  V  Q  V  L  K  L  L  L  N  L  S                   222
KTA CTT ACT GGA AAT GGA AAC ACG AAG GTG CAA GTT TTG AAA CTG CTT TTG AAT TTG NCT  1051


 E  N  P  A  M  T  E  G  L  L  R  A  Q  V  D  S  S  F  L  S                   242
GAA AAT CCA GCC ATG ACA GAA GGA CTT CTC CGT GCC CAA GTG GAT TCA TCA TTC CTT TYC  1111

 L  Y  D  S  H  V  A  K  E  I  L  L  R  V  L  T  L  F  Q  N                   262
CTT TAT GAC AGC CAC GTA GCA AAG GAG ATT CTT CTT CGA GTA CTT ACG CTA TTT CAG AAT  1171

 I  K  N  C  L  K  I  E  G  H  L  A  V  Q  P  T  F  T  E  G                   282
ATA AAG AAC TGC CTC AAA ATA GAA GGC CAT TTA GCT GTG CAG CCT ACT TTC ACT GAA GGT  1231

 S  L  F  F  L  L  H  G  E  E  C  A  Q  K  I  R  A  L  V  D                   302
TCA TTG TTT TTC CTG TTA CAT GGA GAA GAA TGT GCC CAG AAA ATA AGA GCT TTA GTT GAT  1291

 H  H  D  A  E  V  K  E  K  V  V  T  I  I  P  K  I  *                         320
CAC CAT GAT GCA GAG GTG AAG GAA AAG GTT GTA ACA ATA ATA CCC AAA ATC TGA          1345

TTGGTCATATTTTTCCAAAGAGTAATGCAGTCTGGATATAAATGTATTTTCTGTCTTCCTTATAAGGGGATTCTCCCAG  1424

CTGCTAAATTTAAACAGTAAATATCACATTTTGTCATTAACACAGCTATAACTTGCCGTGGTTCTCAGATTTATTTTGG  1503

ACTATTTTGATGCCAAGTGAATATAAGAGCTTGTACTGAAACCATTTATTTCTTTCTATTTTGCTATTTGCAAATGCTT  1582

GTTATCTTCCCTACATGAAGTGGCAGTAACCTTTTTCACATTTAAGCTACCCTTCTACCTTTTGAAGTGATTTGCAGTT  1661

ACTCATCTGAGACAGCATCAGTATTTGACTAAATCATTGTTTCACAACTGAATAGTCTTGTTCTTTTAGTAGCAATGAA  1740

ATCCTAAGCTCTTGAGGCCATTCACCTGCCAACCTGACCATACTGCTTTCAAAAGTCTTTTCTCATCAGTAGAATCTAT  1819
```

FIG. 47 (1 of 2)

TTTGGTCACTTCTAGTCAATGAAAAATGTAAACTTTTAGGAGAGAATGTTTCCTAGGACTCACCCACTCCATTCAATGT 1898

TACATATAAAATAGTGTGATCAATCACAATGTCCATCTTTAGACAGTTGGTTAAATAAATTATCTGGTCTTTGAAAAGA 1977

CCGTGCTGGGCGCGGTGGCTCTTGCCTGTAATCCCAGCACTTTGGGAGGCTGAGGCGGGCAGATCACCTGAGATCGGGA 2056

GTTTGAGACCAAGCCTGACCAATATGGAGAAACCCTGTCTCTACTAAGAATACAAAATTAGCTGGGCATGGTGGTGCAT 2135

GCCTGTAATCCCAGCTACTTGGGAGGCCGAGGCAGGAGAATTGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGGTGAG 2214

ATAGCGCCATTGCACTCCAGCCTGGGCAACAAGAGCAAAACTCTGTCTCAAAAAAAAAAAAAAAATGATGGAGCTCCGAA 2293

TGTGCTTAAGTGGAAAGATATCTATGAAATATGGTGGTTTTTTAAAACACAAAAATTATAGAATATGGGATCCCGTGTG 2372

TGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTTTGAATGAAAAATGCTTATGTATTGACAGAACACTT 2451

CTAGAATGATACCCAAACTCCTGGAGTGGGAGTGGGGAATGCCTTCTACGTACACACTGTTCTACTGTTTGAATTTTTT 2530

AATATGAGCCCAAATTGTATAATCTTTTTTTAATAAAGGGGAGAAAAATCAAAAAAAAAAAAAAA 2595

FIG. 47 (2 OF 2)

Input file T187human123; Output File T187human123.pat
Sequence length 2700

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CCACGCGTCCGGCCAGGGGCGGGAGGGAGGAATGGTTGCTTCACGCCCCGGGGGAAGAGACGGGAAGCTCGGCTCTGGG  79

TTGCGGGCCCCGGCGTCTCCGCGTGGGGCGCACCGTCCGACCCGCCCCTCCCGGTGTGCAGCGCCCCGCACCGCCCCGC  158

CTCGCCTGGGAGAAGCCGCCGGGACGCGCCGGGCTGGAGTGGGCGGTTATAGGCTTTGAGCTAGGCCGTTTCCGGGAGG  237

CGGAGCTCAGACCCCATTTCCTTTCTCCACATCCAGGTCAGGTGGCGTTTGCTGTGGCGGCTAGGCCCGCGTGCGCTGG  316

                                                                    M   G       2
AGACCTCCGCGCTGGCCCCCGCGAGCCTCCTGCCCTGGCCCGGCGCTGCGGCTCTGCCGCGGCGGCAGC ATG GGT     391

 G   P   R   G   A   G   W   V   A   A   G   L   L   L   G   A   G   A   C   Y      22
GGC CCC CGG GGC GCG GGC TGG GTG GCG GCG GGC CTG CTG CTC GGC GCG GGC GCC TGC TAC    451

 C   I   Y   R   L   T   R   G   R   R   R   G   D   R   E   L   G   I   R   S      42
TGC ATT TAC AGG CTG ACC CGG GGT CGG CGG CGG GGC GAC CGC GAG CTC GGG ATA CGC TCT    511

 S   K   S   A   G   A   L   E   E   G   T   S   E   G   Q   L   C   G   R   S      62
TCG AAG TCC GCA GGT GCC CTG GAA GAA GGG ACG TCA GAG GGT CAN TTG TGC GGG CGC TCG    571

 A   R   P   Q   T   G   G   T   W   E   S   Q   W   S   K   T   S   Q   P   E      82
GCC CGG CCT CAG ACN GGA GGT ACC TGG GAG TCA CAG TGG TCC AAG ACC TCG CAN CCT GAA    631

 D   L   T   D   G   S   Y   D   D   V   L   N   A   E   Q   L   Q   K   L   L     102
GAC TTA ACT GAT GGT TCA TAT GAT GAT GTT CTA AAT GCT GAA CAA CTT CAG AAA CTC CTT    691

 Y   L   L   E   S   T   E   D   P   V   I   I   E   R   A   L   I   T   L   G     122
TAC CTG CTG GAG TCA ACG GAG GAT CCT GTA ATT ATT GAA AGA GCT TTG ATT ACT TTG GGT    751

 N   N   A   A   F   S   V   N   Q   I   P   M   K   L   V   T   G   I   T   F     142
AAC AAT GCA GCC TTT TCA GTT AAC CAA ATC CCT ATG AAG TTG GTC ACT GGC ATC ACA TTC    811

 A   I   I   R   E   L   G   G   I   P   I   V   A   N   K   I   N   H   S   N     162
GCT ATT ATT CGT GAA TTG GGT GGT ATT CCA ATT GTT GCA AAC AAA ATC AAC CAT TCC AAC    871

 Q   S   I   K   E   K   A   L   N   A   L   N   N   L   S   V   N   V   E   N     182
CAG AGT ATT AAA GAG AAA GCT TTA AAT GCA CTA AAT AAC CTG AGT GTG AAT GTT GAA AAT    931

 Q   I   K   I   K   I   Y   I   S   Q   V   C   E   D   V   F   S   G   P   L     202
CAA ATC AAG ATA AAG ATA TAC ATC AGT CAA GTA TGT GAG GAT GTC TTC TCT GGT CCT CTG    991

 N   S   A   V   Q   L   A   G   L   T   L   L   T   N   M   T   V   T   N   D     222
AAC TCT GCT GTG CAG CTG GCT GGA CTG ACA TTG TTG ACA AAC ATG ACT GTT ACC AAT GAC   1051

 H   Q   H   M   L   H   S   Y   I   T   D   L   F   Q   V   L   L   T   G   N     242
CAC CAG CAC ATG CTT CAC AGT TAC ATT ACA GAC CTG TTC CAG GTG KTA CTT ACT GGA AAT   1111

 G   N   T   K   V   Q   V   L   K   L   L   L   N   L   S   E   N   P   A   M     262
GGA AAC ACG AAG GTG CAA GTT TTG AAA CTG CTT TTG AAT TTG NCT GAA AAT CCA GCC ATG   1171

 T   E   G   L   L   R   A   Q   V   D   S   S   F   L   S   L   Y   D   S   H     282
ACA GAA GGA CTT CTC CGT GCC CAA GTG GAT TCA TCA TTC CTT TYC CTT TAT GAC AGC CAC   1231

 V   A   K   E   I   L   L   R   V   L   T   L   F   Q   N   I   K   N   C   L     302
GTA GCA AAG GAG ATT CTT CTT CGA GTA CTT ACG CTA TTT CAG AAT ATA AAG AAC TGC CTC   1291

 K   I   E   G   H   L   A   V   Q   P   T   F   T   E   G   S   L   F   F   L     322
AAA ATA GAA GGC CAT TTA GCT GTG CAG CCT ACT TTC ACT GAA GGT TCA TTG TTT TTC CTG   1351

 L   H   G   E   E   C   A   Q   K   I   R   A   L   V   D   H   H   D   A   E     342
TTA CAT GGA GAA GAA TGT GCC CAG AAA ATA AGA GCT TTA GTT GAT CAC CAT GAT GCA GAG   1411

 V   K   E   K   V   V   T   I   I   P   K   I   *                               355
GTG AAG GAA AAG GTT GTA ACA ATA ATA CCC AAA ATC TGA                              1450

TTGGTCATATTTTTCCAAAGAGTAATGCAGTCTGGATATAAATGTATTTTCTGTCTTCCTTATAAGGGGATTCTCCCAG  1529

CTGCTAAATTTAAACAGTAAATATCACATTTTGTCATTAACACAGCTATAACTTGCCGTGGTTCTCAGATTTATTTTGG  1608

ACTATTTTGATGCCAAGTGAATATAAGAGCTTGTACTGAAACCATTTATTTCTTTCTATTTTGCTATTTGCAAATGCTT  1687
```

FIG. 4B (1 of 2)

GTTATCTTCCCTACATGAAGTGGCAGTAACCTTTTTCACATTTAAGCTACCCTTCTACCTTTTGAAGTGATTTGCAGTT 1766

ACTCATCTGAGACAGCATCAGTATTTGACTAAATCATTGTTTCACAACTGAATAGTCTTGTTCTTTTAGTAGCAATGAA 1845

ATCCTAAGCTCTTGAGGCCATTCACCTGCCAACCTGACCATACTGCTTTCAAAAGTCTTTTCTCATCAGTAGAATCTAT 1924

TTTGGTCACTTCTAGTCAATGAAAAATGTAAACTTTTAGGAGAGAATGTTTCCTAGGACTCACCCACTCCATTCAATGT 2003

TACATATAAAATAGTGTGATCAATCACAATGTCCATCTTTAGACAGTTGGTTAAATAAATTATCTGGTCTTTGAAAAGA 2082

CCGTGCTGGGCGCGGTGGCTCTTGCCTGTAATCCCAGCACTTTGGGAGGCTGAGGCGGGCAGATCACCTGAGATCGGGA 2161

GTTTGAGACCAAGCCTGACCAATATGGAGAAACCCTGTCTCTACTAAGAATACAAAATTAGCTGGGCATGGTGGTGCAT 2240

GCCTGTAATCCCAGCTACTTGGGAGGCCGAGGCAGGAGAATTGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGGTGAG 2319

ATAGCGCCATTGCACTCCAGCCTGGGCAACAAGAGCAAAACTCTGTCTCAAAAAAAAAAAAAAAATGATGGAGCTCCGAA 2398

TGTGCTTAAGTGGAAAGATATCTATGAAATATGGTGGTTTTTTAAAACACAAAAATTATAGAATATGGGATCCCGTGTG 2477

TGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTTTGAATGAAAAATGCTTATGTATTGACAGAACACTT 2556

CTAGAATGATACCCAAACTCCTGGAGTGGGAGTGGGGAATGCCTTCTACGTACACACTGTTCTACTGTTTGAATTTTTT 2635

AATATGAGCCCAAATTGTATAATCTTTTTTTAATAAAGGGGAGAAAAATCAAAAAAAAAAAAAAA 2700

FIG 4.9 (2 of 2)

Input file T187human12; Output File T187human12.pat
Sequence length 2523

```
CCACGCGTCCGGCCAGGGGCGGGAGGGAGGAATGGTTGCTTCACGCCCCGGGGGAAGAGACGGGAAGCTCGGCTCTGGG  79

TTGCGGGCCCCGGCGTCTCCGCGTGGGGCGCACCGTCCGACCCGCCCCTCCCGGTGTGCAGCGCCCCGCACCGCCCGC  158

CTCGCCTGGGAGAAGCCGCCGGGACGCGCCGGGCTGGAGTGGGCGGTTATAGGCTTTGAGCTAGGCCGTTTCCGGGAGG  237

CGGAGCTCAGACCCCATTTCCTTTCTCCACATCCAGGTCAGGTGGCGTTTGCTGTGGCGGCTAGGCCCGCGTGCGCTGG  316

                                                                    M  G      2
AGACCTCCGCGCTGGCCCCCGCGAGCCTCCTGCCCTGGCCCGGCGCTGCGGCTCTGCCGCGGCGGCAGC ATG GGT    391

 G  P  R  G  A  G  W  V  A  A  G  L  L  L  G  A  G  A  C  Y      22
GGC CCC CGG GGC GCG GGC TGG GTG GCG GCG GGC CTG CTG CTC GGC GCG GGC GCC TGC TAC  451

 C  I  Y  R  L  T  R  G  R  R  R  G  D  R  E  L  G  I  R  S      42
TGC ATT TAC AGG CTG ACC CGG GGT CGG CGG CGG GGC GAC CGC GAG CTC GGG ATA CGC TCT  511

 S  K  S  A  G  A  L  E  E  G  T  S  E  G  Q  L  C  G  R  S      62
TCG AAG TCC GCA GGT GCC CTG GAA GAA GGG ACG TCA GAG GGT CAN TTG TGC GGG CGC TCG  571

 A  R  P  Q  T  G  G  T  W  E  S  Q  W  S  K  T  S  x  P  E      82
GCC CGG CCT CAG ACN GGA GGT ACC TGG GAG TCA CAG TGG TCC AAG ACC TCG CAN CCT GAA  631

 D  L  T  D  G  S  Y  D  D  V  L  N  A  E  Q  L  Q  K  L  L     102
GAC TTA ACT GAT GGT TCA TAT GAT GAT GTT CTA AAT GCT GAA CAA CTT CAG AAA CTC CTT  691

 Y  L  L  E  S  T  E  D  P  V  I  I  E  R  A  L  I  T  L  G     122
TAC CTG CTG GAG TCA ACG GAG GAT CCT GTA ATT ATT GAA AGA GCT TTG ATT ACT TTG GGT  751

 N  N  A  A  F  S  V  N  Q  I  P  M  K  L  V  T  G  I  T  F     142
AAC AAT GCA GCC TTT TCA GTT AAC CAA ATC CCT ATG AAG TTG GTC ACT GGC ATC ACA TTC  811

 A  I  I  R  E  L  G  G  I  P  I  V  A  N  K  I  N  H  S  N     162
GCT ATT ATT CGT GAA TTG GGT GGT ATT CCA ATT GTT GCA AAC AAA ATC AAC CAT TCC AAC  871

 Q  S  I  K  E  K  A  L  N  A  L  N  N  L  S  V  N  V  E  N     182
CAG AGT ATT AAA GAG AAA GCT TTA AAT GCA CTA AAT AAC CTG AGT GTG AAT GTT GAA AAT  931

 Q  I  K  I  K  V  Q  V  L  K  L  L  L  N  L  S  E  N  P  A     202
CAA ATC AAG ATA AAG GTG CAA GTT TTG AAA CTG CTT TTG AAT TTG NCT GAA AAT CCA GCC  991

 M  T  E  G  L  L  R  A  Q  V  D  S  S  F  L  S  L  Y  D  S     222
ATG ACA GAA GGA CTT CTC CGT GCC CAA GTG GAT TCA TCA TTC CTT TYC CTT TAT GAC AGC 1051

 H  V  A  K  E  I  L  L  R  V  L  T  L  F  Q  N  I  K  N  C     242
CAC GTA GCA AAG GAG ATT CTT CTT CGA GTA CTT ACG CTA TTT CAG AAT ATA AAG AAC TGC 1111

 L  K  I  E  G  H  L  A  V  Q  P  T  F  T  E  G  S  L  F  F     262
CTC AAA ATA GAA GGC CAT TTA GCT GTG CAG CCT ACT TTC ACT GAA GGT TCA TTG TTT TTC 1171

 L  L  H  G  E  E  C  A  Q  K  I  R  A  L  V  D  H  H  D  A     282
CTG TTA CAT GGA GAA GAA TGT GCC CAG AAA ATA AGA GCT TTA GTT GAT CAC CAT GAT GCA 1231

 E  V  K  E  K  V  V  T  I  I  P  K  I  *                       296
GAG GTG AAG GAA AAG GTT GTA ACA ATA ATA CCC AAA ATC TGA                        1273

TTGGTCATATTTTTCCAAAGAGTAATGCAGTCTGGATATAAATGTATTTTCTGTCTTCCTTATAAGGGGATTCTCCCAG 1352

CTGCTAAATTTAAACAGTAAATATCACATTTTGTCATTAACACAGCTATAACTTGCCGTGGTTCTCAGATTTATTTTGG 1431

ACTATTTTGATGCCAAGTGAATATAAGAGCTTGTACTGAAACCATTTATTTCTTTCTATTTTGCTATTTGCAAATGCTT 1510

GTTATCTTCCCTACATGAAGTGGCAGTAACCTTTTTCACATTTAAGCTACCCTTCTACCTTTTGAAGTGATTTGCAGTT 1589

ACTCATCTGAGACAGCATCAGTATTTGACTAAATCATTGTTTCACAACTGAATAGTCTTGTTCTTTTAGTAGCAATGAA 1668

ATCCTAAGCTCTTGAGGCCATTCACCTGCCAACCTGACCATACTGCTTTCAAAAGTCTTTTCTCATCAGTAGAATCTAT 1747
```

FIG. 4I (1 of 2)

TTTGGTCACTTCTAGTCAATGAAAAATGTAAACTTTTAGGAGAGAATGTTTCCTAGGACTCACCCACTCCATTCAATGT 1826

TACATATAAAATAGTGTGATCAATCACAATGTCCATCTTTAGACAGTTGGTTAAATAAATTATCTGGTCTTTGAAAAGA 1905

CCGTGCTGGGCGCGGTGGCTCTTGCCTGTAATCCCAGCACTTTGGGAGGCTGAGGCGGGCAGATCACCTGAGATCGGGA 1984

GTTTGAGACCAAGCCTGACCAATATGGAGAAACCCTGTCTCTACTAAGAATACAAAATTAGCTGGGCATGGTGGTGCAT 2063

GCCTGTAATCCCAGCTACTTGGGAGGCCGAGGCAGGAGAATTGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGGTGAG 2142

ATAGCGCCATTGCACTCCAGCCTGGGCAACAAGAGCAAAACTCTGTCTCAAAAAAAAAAAAAAAATGATGGAGCTCCGAA 2221

TGTGCTTAAGTGGAAAGATATCTATGAAATATGGTGGTTTTTTAAAACACAAAAATTATAGAATATGGGATCCCGTGTG 2300

TGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTTTGAATGAAAAATGCTTATGTATTGACAGAACACTT 2379

CTAGAATGATACCCAAACTCCTGGAGTGGGAGTGGGGAATGCCTTCTACGTACACACTGTTCTACTGTTTGAATTTTTT 2458

AATATGAGCCCAAATTGTATAATCTTTTTTTAATAAAGGGGAGAAAAATCAAAAAAAAAAAAAAA 2523

```
Input file T187human2; Output File Thuman2.pat
Sequence length 2418

CCACGCGTCCGGCCAGGGGCGGGAGGGAGGAATGGTTGCTTCACGCCCCGGGGGAAGAGACGGGAAGCTCGGCTCTGGG  79

TTGCGGGCCCCGGCGTCTCCGCGTGGGGCGCACCGTCCGACCCGCCCCTCCCGGTGTGCAGCGCCCCGCACCGCCCCGC  158

CTCGCCTGGGAGAAGCCGCCGGGACGCGCCGGGCTGGAGTGGGCGGTTATAGGCTTTGAGCTAGGCCGTTTCCGGGAGG  237

CGGAGCTCAGACCCCATTTCCTTTCTCCACATCCAGGTCAGGTGGCGTTTGCTGTGGCGGCTAGGCCCGCGTGCGCTGG  316

                                                                  M  G      2
AGACCTCCGCGCTGGCCCCCGCGAGCCTCCTGCCCTGGCCCGGCGCTGCGGCTCTGCCGCGGCGGCAGC ATG GGT    391

 G  P  R  G  A  G  W  V  A  A  G  L  L  L  G  A  G  A  C  Y    22
GGC CCC CGG GGC GCG GGC TGG GTG GCG GCG GGC CTG CTG CTC GGC GCG GGC GCC TGC TAC  451

 C  I  Y  R  L  T  R  G  R  R  R  G  D  R  E  L  G  I  R  S    42
TGC ATT TAC AGG CTG ACC CGG GGT CGG CGG CGG GGC GAC CGC GAG CTC GGG ATA CGC TCT  511

 S  K  S  A  E  D  L  T  D  G  S  Y  D  D  V  L  N  A  E  Q    62
TCG AAG TCC GCA GAA GAC TTA ACT GAT GGT TCA TAT GAT GAT GTT CTA AAT GCT GAA CAA  571

 L  Q  K  L  L  Y  L  L  E  S  T  E  D  P  V  I  I  E  R  A    82
CTT CAG AAA CTC CTT TAC CTG CTG GAG TCA ACG GAG GAT CCT GTA ATT ATT GAA AGA GCT  631

 L  I  T  L  G  N  N  A  A  F  S  V  N  Q  I  P  M  K  L  V   102
TTG ATT ACT TTG GGT AAC AAT GCA GCC TTT TCA GTT AAC CAA ATC CCT ATG AAG TTG GTC  691

 T  G  I  T  F  A  I  I  R  E  L  G  G  I  P  I  V  A  N  K   122
ACT GGC ATC ACA TTC GCT ATT ATT CGT GAA TTG GGT GGT ATT CCA ATT GTT GCA AAC AAA  751

 I  N  H  S  N  Q  S  I  K  E  K  A  L  N  A  L  N  N  L  S   142
ATC AAC CAT TCC AAC CAG AGT ATT AAA GAG AAA GCT TTA AAT GCA CTA AAT AAC CTG AGT  811

 V  N  V  E  N  Q  I  K  I  K  V  Q  V  L  K  L  L  L  N  L   162
GTG AAT GTT GAA AAT CAA ATC AAG ATA AAG GTG CAA GTT TTG AAA CTG CTT TTG AAT TTG  871

 S  E  N  P  A  M  T  E  G  L  L  R  A  Q  V  D  S  S  F  L   182
NCT GAA AAT CCA GCC ATG ACA GAA GGA CTT CTC CGT GCC CAA GTG GAT TCA TCA TTC CTT  931

 S  L  Y  D  S  H  V  A  K  E  I  L  L  R  V  L  T  L  F  Q   202
TYC CTT TAT GAC AGC CAC GTA GCA AAG GAG ATT CTT CTT CGA GTA CTT ACG CTA TTT CAG  991

 N  I  K  N  C  L  K  I  E  G  H  L  A  V  Q  P  T  F  T  E   222
AAT ATA AAG AAC TGC CTC AAA ATA GAA GGC CAT TTA GCT GTG CAG CCT ACT TTC ACT GAA 1051

 G  S  L  F  F  L  L  H  G  E  E  C  A  Q  K  I  R  A  L  V   242
GGT TCA TTG TTT TTC CTG TTA CAT GGA GAA GAA TGT GCC CAG AAA ATA AGA GCT TTA GTT 1111

 D  H  H  D  A  E  V  K  E  K  V  V  T  I  I  P  K  I  *      261
GAT CAC CAT GAT GCA GAG GTG AAG GAA AAG GTT GTA ACA ATA ATA CCC AAA ATC TGA     1168

TTGGTCATATTTTTCCAAAGAGTAATGCAGTCTGGATATAAATGTATTTTCTGTCTTCCTTATAAGGGGATTCTCCCAG  1247

CTGCTAAATTTAAACAGTAAATATCACATTTTGTCATTAACACAGCTATAACTTGCCGTGGTTCTCAGATTTATTTTGG  1326

ACTATTTTGATGCCAAGTGAATATAAGAGCTTGTACTGAAACCATTTATTTCTTTCTATTTTGCTATTTGCAAATGCTT  1405

GTTATCTTCCCTACATGAAGTGGCAGTAACCTTTTTCACATTTAAGCTACCCTTCTACCTTTTGAAGTGATTTGCAGTT  1484

ACTCATCTGAGACAGCATCAGTATTTGACTAAATCATTGTTTCACAACTGAATAGTCTTGTTCTTTTAGTAGCAATGAA  1563

ATCCTAAGCTCTTGAGGCCATTCACCTGCCAACCTGACCATACTGCTTTCAAAAGTCTTTTCTCATCAGTAGAATCTAT  1642

TTTGGTCACTTCTAGTCAATGAAAAATGTAAACTTTTAGGAGAGAATGTTTCCTAGGACTCACCCACTCCATTCAATGT  1721

TACATATAAAATAGTGTGATCAATCACAATGTCCATCTTTAGACAGTTGGTTAAATAAATTATCTGGTCTTTGAAAAGA  1800

CCGTGCTGGGCGCGGTGGCTCTTGCCTGTAATCCCAGCACTTTGGGAGGCTGAGGCGGGCAGATCACCTGAGATCGGGA  1879

GTTTGAGACCAAGCCTGACCAATATGGAGAAACCCTGTCTCTACTAAGAATACAAAATTAGCTGGGCATGGTGGTGCAT  1958
```

FIG. 50 (1 of 2)

GCCTGTAATCCCAGCTACTTGGGAGGCCGAGGCAGGAGAATTGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGGTGAG 2037

ATAGCGCCATTGCACTCCAGCCTGGGCAACAAGAGCAAAACTCTGTCTCAAAAAAAAAAAAAAAATGATGGAGCTCCGAA 2116

TGTGCTTAAGTGGAAAGATATCTATGAAATATGGTGGTTTTTTAAAACACAAAAATTATAGAATATGGGATCCCGTGTG 2195

TGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTTTGAATGAAAAATGCTTATGTATTGACAGAACACTT 2274

CTAGAATGATACCCAAACTCCTGGAGTGGGAGTGGGGAATGCCTTCTACGTACACACTGTTCTACTGTTTGAATTTTTT 2353

AATATGAGCCCAAATTGTATAATCTTTTTTTAATAAAGGGGAGAAAAATCAAAAAAAAAAAAAAA 2418

FIG. 50 (CONT'D)

Input file T187human3; Output File T187human3.pat
Sequence length 2562

```
CCACGCGTCCGGCCAGGGGCGGGAGGGAGGAATGGTTGCTTCACGCCCCGGGGGAAGAGACGGGAAGCTCGGCTCTGGG  79

TTGCGGGCCCCGGCGTCTCCGCGTGGGGCGCACCGTCCGACCCGCCCCTCCCGGTGTGCAGCGCCCCGCACCGCCCCGC  158

CTCGCCTGGGAGAAGCCGCCGGGACGCGCCGGGCTGGAGTGGGCGGTTATAGGCTTTGAGCTAGGCCGTTTCCGGGAGG  237

CGGAGCTCAGACCCCATTTCCTTTCTCCACATCCAGGTCAGGTGGCGTTTGCTGTGGCGGCTAGGCCCGCGTGCGCTGG  316

                                                                    M  G      2
AGACCTCCGCGCTGGCCCCCGCGAGCCTCCTGCCCTGGCCCGGCGCTGCGGCTCTGCCGCGGCGGCAGC ATG GGT    391

 G  P  R  G  A  G  W  V  A  A  G  L  L  L  G  A  G  A  C  Y    22
GGC CCC CGG GGC GCG GGC TGG GTG GCG GCG GGC CTG CTG CTC GGC GCG GGC GCC TGC TAC  451

 C  I  Y  R  L  T  R  G  R  R  R  G  D  R  E  L  G  I  R  S    42
TGC ATT TAC AGG CTG ACC CGG GGT CGG CGG CGG GGC GAC CGC GAG CTC GGG ATA CGC TCT  511

 S  K  S  A  E  D  L  T  D  G  S  Y  D  D  V  L  N  A  E  Q    62
TCG AAG TCC GCA GAA GAC TTA ACT GAT GGT TCA TAT GAT GAT GTT CTA AAT GCT GAA CAA  571

 L  Q  K  L  L  Y  L  L  E  S  T  E  D  P  V  I  I  E  R  A    82
CTT CAG AAA CTC CTT TAC CTG CTG GAG TCA ACG GAG GAT CCT GTA ATT ATT GAA AGA GCT  631

 L  I  T  L  G  N  N  A  A  F  S  V  N  Q  A  I  I  R  E  L   102
TTG ATT ACT TTG GGT AAC AAT GCA GCC TTT TCA GTT AAC CAA GCT ATT ATT CGT GAA TTG  691

 G  G  I  P  I  V  A  N  K  I  N  H  S  N  Q  S  I  K  E  K   122
GGT GGT ATT CCA ATT GTT GCA AAC AAA ATC AAC CAT TCC AAC CAG AGT ATT AAA GAG AAA  751

 A  L  N  A  L  N  N  L  S  V  N  V  E  N  Q  I  K  I  K  I   142
GCT TTA AAT GCA CTA AAT AAC CTG AGT GTG AAT GTT GAA AAT CAA ATC AAG ATA AAG ATA  811

 Y  I  S  Q  V  C  E  D  V  F  S  G  P  L  N  S  A  V  Q  L   162
TAC ATC AGT CAA GTA TGT GAG GAT GTC TTC TCT GGT CCT CTG AAC TCT GCT GTG CAG CTG  871

 A  G  L  T  L  L  T  N  M  T  V  T  N  D  H  Q  H  M  L  H   182
GCT GGA CTG ACA TTG TTG ACA AAC ATG ACT GTT ACC AAT GAC CAC CAG CAC ATG CTT CAC  931

 S  Y  I  T  D  L  F  Q  V  L  L  T  G  N  G  N  T  K  V  Q   202
AGT TAC ATT ACA GAC CTG TTC CAG GTG KTA CTT ACT GGA AAT GGA AAC ACG AAG GTG CAA  991

 V  L  K  L  L  L  N  L  S  E  N  P  A  M  T  E  G  L  L  R   222
GTT TTG AAA CTG CTT TTG AAT TTG NCT GAA AAT CCA GCC ATG ACA GAA GGA CTT CTC CGT  1051

 A  Q  V  D  S  S  F  L  S  L  Y  D  S  H  V  A  K  E  I  L   242
GCC CAA GTG GAT TCA TCA TTC CTT TYC CTT TAT GAC AGC CAC GTA GCA AAG GAG ATT CTT  1111

 L  R  V  L  T  L  F  Q  N  I  K  N  C  L  K  I  E  G  H  L   262
CTT CGA GTA CTT ACG CTA TTT CAG AAT ATA AAG AAC TGC CTC AAA ATA GAA GGC CAT TTA  1171

 A  V  Q  P  T  F  T  E  G  S  L  F  F  L  L  H  G  E  E  C   282
GCT GTG CAG CCT ACT TTC ACT GAA GGT TCA TTG TTT TTC CTG TTA CAT GGA GAA GAA TGT  1231

 A  Q  K  I  R  A  L  V  D  H  H  D  A  E  V  K  E  K  V  V   302
GCC CAG AAA ATA AGA GCT TTA GTT GAT CAC CAT GAT GCA GAG GTG AAG GAA AAG GTT GTA  1291

 T  I  I  P  K  I  *                                          309
ACA ATA ATA CCC AAA ATC TGA                                   1312

TTGGTCATATTTTTCCAAAGAGTAATGCAGTCTGGATATAAATGTATTTTCTGTCTTCCTTATAAGGGGATTCTCCCAG  1391

CTGCTAAATTTAAACAGTAAATATCACATTTTGTCATTAACACAGCTATAACTTGCCGTGGTTCTCAGATTTATTTTGG  1470

ACTATTTTGATGCCAAGTGAATATAAGAGCTTGTACTGAAACCATTTATTTCTTTCTATTTTGCTATTTGCAAATGCTT  1549

GTTATCTTCCCTACATGAAGTGGCAGTAACCTTTTTCACATTTAAGCTACCCTTCTACCTTTTGAAGTGATTTGCAGTT  1628

ACTCATCTGAGACAGCATCAGTATTTGACTAAATCATTGTTTCACAACTGAATAGTCTTGTTCTTTTAGTAGCAATGAA  1707
```

Fig. 5I (sheet 2)

ATCCTAAGCTCTTGAGGCCATTCACCTGCCAACCTGACCATACTGCTTTCAAAAGTCTTTTCTCATCAGTAGAATCTAT 1786

TTTGGTCACTTCTAGTCAATGAAAAATGTAAACTTTTAGGAGAGAATGTTTCCTAGGACTCACCCACTCCATTCAATGT 1865

TACATATAAAATAGTGTGATCAATCACAATGTCCATCTTTAGACAGTTGGTTAAATAAATTATCTGGTCTTTGAAAAGA 1944

CCGTGCTGGGCGCGGTGGCTCTTGCCTGTAATCCCAGCACTTTGGGAGGCTGAGGCGGGCAGATCACCTGAGATCGGGA 2023

GTTTGAGACCAAGCCTGACCAATATGGAGAAACCCTGTCTCTACTAAGAATACAAAATTAGCTGGGCATGGTGGTGCAT 2102

GCCTGTAATCCCAGCTACTTGGGAGGCCGAGGCAGGAGAATTGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGGTGAG 2181

ATAGCGCCATTGCACTCCAGCCTGGGCAACAAGAGCAAAACTCTGTCTCAAAAAAAAAAAAAAAATGATGGAGCTCCGAA 2260

TGTGCTTAAGTGGAAAGATATCTATGAAATATGGTGGTTTTTTAAAACACAAAAATTATAGAATATGGGATCCCGTGTG 2339

TGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTTTGAATGAAAAATGCTTATGTATTGACAGAACACTT 2418

CTAGAATGATACCCAAACTCCTGGAGTGGGAGTGGGGAATGCCTTCTACGTACACACTGTTCTACTGTTTGAATTTTTT 2497

AATATGAGCCCAAATTGTATAATCTTTTTTTAATAAAGGGGAGAAAAATCAAAAAAAAAAAAAAA 2562

FIG. 31 (2 of 2)

Input file T187human; Output File T187human.pat
Sequence length 2385

```
CCACGCGTCCGGCCAGGGGCGGGAGGGAGGAATGGTTGCTTCACGCCCCGGGGGAAGAGACGGGAAGCTCGGCTCTGGG  79

TTGCGGGCCCCGGCGTCTCCGCGTGGGGCGCACCGTCCGACCCGCCCCTCCCGGTGTGCAGCGCCCCGCACCGCCCCGC  158

CTCGCCTGGGAGAAGCCGCCGGGACGCGCCGGGCTGGAGTGGGCGGTTATAGGCTTTGAGCTAGGCCGTTTCCGGGAGG  237

CGGAGCTCAGACCCCATTTCCTTTCTCCACATCCAGGTCAGGTGGCGTTTGCTGTGGCGGCTAGGCCCGCGTGCGCTGG  316

                                                                    M  G      2
AGACCTCCGCGCTGGCCCCCGCGAGCCTCCTGCCCTGGCCCGGCGCTGCGGCTCTGCCGCGGCGGCAGC ATG GGT    391

 G  P  R  G  A  G  W  V  A  A  G  L  L  L  G  A  G  A  C  Y    22
GGC CCC CGG GGC GCG GGC TGG GTG GCG GCG GGC CTG CTG CTC GGC GCG GGC GCC TGC TAC  451

 C  I  Y  R  L  T  R  G  R  R  R  G  D  R  E  L  G  I  R  S    42
TGC ATT TAC AGG CTG ACC CGG GGT CGG CGG CGG GGC GAC CGC GAG CTC GGG ATA CGC TCT  511

 S  K  S  A  E  D  L  T  D  G  S  Y  D  D  V  L  N  A  E  Q    62
TCG AAG TCC GCA GAA GAC TTA ACT GAT GGT TCA TAT GAT GAT GTT CTA AAT GCT GAA CAA  571

 L  Q  K  L  L  Y  L  L  E  S  T  E  D  P  V  I  I  E  R  A    82
CTT CAG AAA CTC CTT TAC CTG CTG GAG TCA ACG GAG GAT CCT GTA ATT ATT GAA AGA GCT  631

 L  I  T  L  G  N  N  A  A  F  S  V  N  Q  A  I  I  R  E  L   102
TTG ATT ACT TTG GGT AAC AAT GCA GCC TTT TCA GTT AAC CAA GCT ATT ATT CGT GAA TTG  691

 G  G  I  P  I  V  A  N  K  I  N  H  S  N  Q  S  I  K  E  K   122
GGT GGT ATT CCA ATT GTT GCA AAC AAA ATC AAC CAT TCC AAC CAG AGT ATT AAA GAG AAA  751

 A  L  N  A  L  N  N  L  S  V  N  V  E  N  Q  I  K  I  K  V   142
GCT TTA AAT GCA CTA AAT AAC CTG AGT GTG AAT GTT GAA AAT CAA ATC AAG ATA AAG GTG  811

 Q  V  L  K  L  L  L  N  L  S  E  N  P  A  M  T  E  G  L  L   162
CAA GTT TTG AAA CTG CTT TTG AAT TTG NCT GAA AAT CCA GCC ATG ACA GAA GGA CTT CTC  871

 R  A  Q  V  D  S  S  F  L  S  L  Y  D  S  H  V  A  K  E  I   182
CGT GCC CAA GTG GAT TCA TCA TTC CTT TYC CTT TAT GAC AGC CAC GTA GCA AAG GAG ATT  931

 L  L  R  V  L  T  L  F  Q  N  I  K  N  C  L  K  I  E  G  H   202
CTT CTT CGA GTA CTT ACG CTA TTT CAG AAT ATA AAG AAC TGC CTC AAA ATA GAA GGC CAT  991

 L  A  V  Q  P  T  F  T  E  G  S  L  F  F  L  L  H  G  E  E   222
TTA GCT GTG CAG CCT ACT TTC ACT GAA GGT TCA TTG TTT TTC CTG TTA CAT GGA GAA GAA 1051

 C  A  Q  K  I  R  A  L  V  D  H  H  D  A  E  V  K  E  K  V   242
TGT GCC CAG AAA ATA AGA GCT TTA GTT GAT CAC CAT GAT GCA GAG GTG AAG GAA AAG GTT 1111

 V  T  I  I  P  K  I  *                                        250
GTA ACA ATA ATA CCC AAA ATC TGA                                1135

TTGGTCATATTTTTCCAAAGAGTAATGCAGTCTGGATATAAATGTATTTTCTGTCTTCCTTATAAGGGGATTCTCCCAG  1214

CTGCTAAATTTAAACAGTAAATATCACATTTTGTCATTAACACAGCTATAACTTGCCGTGGTTCTCAGATTTATTTTGG  1293

ACTATTTTGATGCCAAGTGAATATAAGAGCTTGTACTGAAACCATTTATTTCTTTCTATTTTGCTATTTGCAAATGCTT  1372

GTTATCTTCCCTACATGAAGTGGCAGTAACCTTTTTCACATTTAAGCTACCCTTCTACCTTTTGAAGTGATTTGCAGTT  1451

ACTCATCTGAGACAGCATCAGTATTTGACTAAATCATTGTTTCACAACTGAATAGTCTTGTTCTTTTAGTAGCAATGAA  1530

ATCCTAAGCTCTTGAGGCCATTCACCTGCCAACCTGACCATACTGCTTTCAAAAGTCTTTTCTCATCAGTAGAATCTAT  1609

TTTGGTCACTTCTAGTCAATGAAAAATGTAAACTTTTAGGAGAGAATGTTTCCTAGGACTCACCCACTCCATTCAATGT  1688

TACATATAAAATAGTGTGATCAATCACAATGTCCATCTTTAGACAGTTGGTTAAATAAATTATCTGGTCTTTGAAAAGA  1767

CCGTGCTGGGCGCGGTGGCTCTTGCCTGTAATCCCAGCACTTTGGGAGGCTGAGGCGGGCAGATCACCTGAGATCGGGA  1846

GTTTGAGACCAAGCCTGACCAATATGGAGAAACCCTGTCTCTACTAAGAATACAAAATTAGCTGGGCATGGTGGTGCAT  1925
```

FIG 5L (1 OF 2)

GCCTGTAATCCCAGCTACTTGGGAGGCCGAGGCAGGAGAATTGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGGTGAG 2004

ATAGCGCCATTGCACTCCAGCCTGGGCAACAAGAGCAAAACTCTGTCTCAAAAAAAAAAAAAAAATGATGGAGCTCCGAA 2083

TGTGCTTAAGTGGAAAGATATCTATGAAATATGGTGGTTTTTTAAAACACAAAAATTATAGAATATGGGATCCCGTGTG 2162

TGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTTTGAATGAAAAATGCTTATGTATTGACAGAACACTT 2241

CTAGAATGATACCCAAACTCCTGGAGTGGGAGTGGGGAATGCCTTCTACGTACACACTGTTCTACTGTTTGAATTTTTT 2320

AATATGAGCCCAAATTGTATAATCTTTTTTTAATAAAGGGGAGAAAAATCAAAAAAAAAAAAAAA 2385

FIG 5E (2 of 2)

Input file T181AtmX181a; Output File T181AtmX181a.pat
Sequence length 3919

```
GGGGTGTGGCGGTTTCTACGGTTGCACGGGGGGTTCGGCTGTGTACGGAGCGCCTGGAGGGACAGCCTGGATACAGGTTC  79

     M  A  Q  L  G  A  V  V  A  V  A  S  S  F  F  C  A  S        18
ACTG ATG GCT CAG TTG GGA GCT GTT GTG GCC GTG GCT TCC AGT TTC TTT TGT GCA TCT        137

  L  F  S  A  V  H  K  I  E  E  G  H  I  G  V  Y  Y  R  G  G     38
CTC TTC TCA GCT GTG CAC AAG ATA GAA GAG GGA CAT ATT GGA GTA TAT TAC AGA GGT GGT    197

  A  L  L  T  S  T  S  G  P  G  F  H  L  M  L  P  F  I  T  S     58
GCC CTG CTG ACC TCC ACC AGT GGC CCG GGT TTC CAT CTC ATG CTC CCG TTC ATC ACA TCC    257

  Y  K  S  V  Q  T  T  L  Q  T  D  E  V  K  N  V  P  C  G  T     78
TAT AAG TCT GTA CAG ACC ACT CTC CAA ACT GAT GAA GTG AAG AAC GTA CCA TGT GGA ACC    317

  S  G  G  V  M  I  Y  F  D  R  I  E  V  V  N  F  L  V  P  N     98
AGT GGT GGT GTG ATG ATC TAC TTT GAC AGA ATT GAA GTG GTG AAC TTC CTG GTC CCA AAT    377

  A  V  Y  D  I  V  K  N  Y  T  A  D  Y  D  K  A  L  I  F  N    118
GCA GTG TAT GAT ATA GTG AAG AAC TAT ACT GCA GAC TAT GAC AAG GCC CTC ATC TTC AAC    437

  K  I  H  H  E  L  N  Q  F  C  S  V  H  T  L  Q  E  V  Y  I    138
AAG ATC CAT CAT GAG CTT AAC CAG TTC TGC AGC GTT CAT ACT CTT CAG GAA GTC TAT ATC    497

  E  L  F  D  Q  I  D  E  N  L  K  L  A  L  Q  Q  D  L  T  S    158
GAG CTG TTT GAT CAA ATT GAT GAA AAC CTC AAG TTG GCT TTG CAG CAG GAC CTG ACT TCC    557

  M  A  P  G  L  V  I  Q  A  V  R  V  T  K  P  N  I  P  E  A    178
ATG GCC CCT GGG CTG GTT ATC CAA GCT GTG CGA GTG ACA AAG CCC AAT ATA CCT GAG GCA    617

  I  R  R  N  Y  E  L  M  E  S  E  K  T  K  L  L  I  A  A  Q    198
ATC CGC AGG AAC TAT GAG CTG ATG GAA AGC GAG AAG ACG AAG CTT CTC ATT GCA GCC CAG    677

  K  Q  K  V  V  E  K  E  A  E  T  E  R  K  K  A  L  I  E  A    218
AAG CAG AAG GTG GTG GAA AAG GAG GCA GAA ACA GAG AGG AAG AAG GCC CTC ATT GAG GCA    737

  E  K  V  A  Q  V  A  E  I  T  Y  G  Q  K  V  M  E  K  E  T    238
GAA AAA GTG GCA CAG GTT GCA GAA ATC ACC TAT GGG CAA AAG GTG ATG GAG AAG GAG ACA    797

  E  K  K  I  S  E  I  E  D  A  A  F  L  A  R  E  K  A  K  A    258
GAG AAG AAG ATC TCA GAA ATT GAA GAT GCT GCG TTC CTG GCC CGG GAG AAG GCG AAG GCC    857

  D  A  E  C  Y  T  A  L  K  I  A  E  A  N  K  L  K  L  T  P    278
GAC GCT GAG TGC TAC ACA GCG CTG AAG ATC GCA GAA GCA AAT AAG CTC AAG CTG ACT CCA    917

  E  Y  L  Q  L  M  K  Y  K  A  I  A  S  N  S  K  I  Y  F  G    298
GAA TAC CTG CAG CTG ATG AAG TAC AAG GCC ATT GCT TCC AAC AGC AAG ATT TAC TTC GGC    977

  K  D  I  P  N  M  F  M  D  S  A  G  G  L  G  K  Q  F  E  G    318
AAA GAC ATC CCC AAC ATG TTT ATG GAT TCC GCA GGG GGG CTG GGC AAG CAG TTT GAG GGG   1037

  L  S  D  D  K  L  G  F  G  L  E  D  E  P  L  E  A  P  T  K    338
CTG AGC GAC GAC AAG CTG GGC TTT GGC CTA GAA GAT GAG CCC CTC GAG GCA CCC ACA AAG   1097

  E  N  *                                                        341
GAG AAC TGA                                                     1106

GGAAACACTGTCTGCAAGCTCTGCTCGGGCAGCTTAGAGAGAGCTGTATTCTTTAAGATGAGACAGAGCAAAGCGCTCC  1185

TCCTTTCCACACTACCTTCCTTGACTCTTCTTACTGTGGTTAAAAAGGAAGAAATGGACACAAACTTACCCCCTTCTGG  1264

GAAGGGAGAGCAGATGGAGAGTTGTTTTTTGGGTTTATTTTTAATTCAGGTAAGTAAGTTGTATGACTTCTGAGAAGGT  1343

GTATGCACCGTAGATTTGACCTCTGACCTGCAGACACCAACATTGTCACTTTGAAGCTGGTTTAAGTGGAGCTACTGTC  1422

AGTATGAAGAGGGAGAGTGTGTGCTGCCTCCTCGTGCTTGAATTCCTTCAGGGAAAAGTGTACTCCACAGTTCTCTCCC  1501

TTGCCTCTAGTGTAGGCAGTGTCTGCGTGTGGGGCTCGTGACAGAAGGCCGTCTGCTGCGGAACATGAGCTGCAGAGAG  1580

CGTTGGCCGGCTGGGCTTTTTGACTGAGTGGATTACTTGAGAGTTAAGCTGTCTTGAGCCCTTTTTAGGAAGAACTTGG  1659

TGCTAGGTTTTGCAAGGTTTTCTACACACTGTACTCTGCTCTAGTGTTTGTTGGCTACATCTCACCGCAGCAGGGCTTG  1738
```

Fig. 5B (1 of 2)

GTCACACCACACACTCCTTTTCCGTACTTTGACCTGATCTGTGATTTCATTTCTTCTTGAATAATCTATTCATGAGTTG 1817

CACTCAGCGTTAAGATGGGAACAAACAAGTGCTGTTAGCTGATGACGTAGCTCCTTATACCCCTTAGCACTGTGGTGCT 1896

GTGTGGCTAATTATGCGTATGCTTTTGAGACCAAACATCTTTATCATTATGGAGATTCTTCATTGAAGAGCCCTTAACA 1975

CTGTGGAGAAGGGCCCAGCCAGATGACACCCAAGTAGTAGTGCCTGTGGCCTGTGCTGGGGGCTTTGTCTGACACTGATG 2054

AAGAGAGCAGGCAGCCACTTGAGAGTCGGCTCCAGTGAGTCACCCTAGGAAACTGAGAATGCGAAGAATAGATATGAGA 2133

GAAAGGGATTTCTTATCCTGAAATTGCACTGGGGGTGGGGCTCTACCATGGCCTGTGAGTGCACACAGAATGCCTCTGT 2212

GGAGGGCAGCTCTGCAGGTAATCTGCAGACATGGCAGTACCCTGTGCAACCATGACTGGCTCTAGCTTAGGACTTGGCC 2291

TTGTTAGCTGGTCCCCTACCTCATCCTCCCCCCACACAAAGCACCTACTGTTCTCTCTTAGGTGACTACTATAAATGGT 2370

ATTTTCTGGCATCAATTCCCACCTCAGTTTTGGTTTTGTAAGTCGGGCCAGTTTGCTCCTAAGTGGCACCAGACTTGTC 2449

AGGTATTTGGGAAGCATTCAGCCGACCCAAAAAGAGGCAGGGTTCACTGTGCTTACTTCAGATGTTCCCTTCTCTGTCC 2528

TGACTCCTCAGGCCACTGACCCTGGCCACACTGTACAAACTACAAAATGTTCCTGAAAAGGACATTTTAATGTGCTCAA 2607

AAGCTCTTGCAAAAGTGGGTTTTTTTTCCCCAAGACCAACTCATCTTCTTCTCATTTGTTGCTGCTAACCACTTGTTGA 2686

GAGCAACGTGCTATACCCAGCATCCTCTCTTGTACGTGCACCTGAGAAAACACTACTTCAGTGGAGTCGGTGCAGGAGG 2765

GAGGGTACCCCGCCATCCAGCGCCCTCCTAGCCCGAGAGGCTCTGTAACTAGCATTCTGAGAGCTCATCCCTCCATTAC 2844

AAAGAGCCACAGTAAAGTCCTGCTGCAGCTGCTCCTTCCCTGCCCCTTTAATGTCACTTCTTTAACAGAACAGAAATGT 2923

CCCCATGTCATAGCATAAATTCAGTAGCTATTGGTATCTGTCCCAGCAGTAAAATCATGGAACTCAGATGTCTTTTTAG 3002

CATGGGATGCCTAGCCCATCTGTCTTTATGACCTTGTTTTTTGTAATACTATAAAATCTGACTTAGGCATTTGAATTCT 3081

AAACATGTAAAATGTGATAAGCCTGCAGTTTTGTAGGCAGTGAATTCATAGCTGCTATTTTTAAGTAGAACTTCTATCA 3160

AAATACGTTAACCGTTTGTAAAATTCAGTTTTTGTAGGACTTTCCCAAGGCCCAGCCACCTTGGTAGAATGCTTCTCAC 3239

TCACTAAATGTTGCAGAAGCAATTTATATTCCATATAGGTTTTTAATCACTTTTCAATATATGGTTAGAATGTTTGTAA 3318

GGAAGCCTAAGTTTAATAATTTTTATATAACTAAAAATAGGTGTGGAGGACTCAGTGTGGGTACTGAGGAGGAATGAAG 3397

TGCTCTGAAAAGGGAGGTGTATAAACGGCCTGTGGGGCCGTGTGTCTTGTGAAAGTGAGATAGCCGTGCTTACTGACCT 3476

GGGCTGTCGTCAGCTGGCCGTCGGTAAACTACCTGGACAATAGCCCCTCTGTCTGGGAACTTTACCTACTTCCTTGTCC 3555

TCAGTGGGCTTCTAGCCACTGTTTGTTTCCTTATAAAAGCTGTAATGGGCAATCATGTGTTTGTACTTCCATTCCTTTT 3634

TATCTCTACTTCTGTGTAAACTGGTGATTGAATAGTTAAAGCAATTTTTTCAGTGTGCCCCAAGGGCATTAATGAGCCT 3713

TTATAACTGAGAAATGATTCTTGTTATAGTAATTATTCCATAAATGATACCACTAGATAAATTACCTTGGGTTAATAGC 3792

TCCAGGATTTGTTTCAGACAACAAAAAAAGGTCTCAATGTGAATATACTTACATTTTGGATTTAATTTCAGTCTTGCTA 3871

AATAAAATGTTTTTGTCTTTTTTTGATTAAGGTAAAAAAAAAAAAAAA 3919

FIG. 53 (2 of 2)

Input file T182mouse; Output File T182mouse.pat
Sequence length 3087

```
                                                  M  N  M  T  Q  A  R  L        8
GGAACCCCGCGTCCGGNGATGCGTCACTGACCGGAGGAACAAGG ATG AAT ATG ACT CAA GCC CGG CTT    68

 L  V  A  A  V  V  G  L  V  A  I  L  L  Y  A  S  I  H  K  I     28
CTG GTG GCT GCA GTG GTG GGG TTG GTG GCG ATC CTC CTG TAC GCC TCC ATC CAC AAG ATC   128

 E  E  G  H  L  A  V  Y  Y  R  G  G  A  L  L  T  S  P  S  G     48
GAA GAG GGA CAC TTG GCC GTG TAC TAC AGG GGA GGA GCT TTG CTA ACG AGC CCC AGT GGA   188

 P  G  Y  H  I  M  L  P  F  I  T  T  F  R  S  V  Q  T  T  L     68
CCA GGC TAT CAT ATC ATG TTG CCT TTC ATT ACA ACA TTC AGA TCT GTG CAG ACA ACA CTA   248

 Q  T  D  E  V  K  N  V  P  C  G  T  S  G  G  V  M  I  Y  I     88
CAA ACG GAT GAA GTT AAA AAT GTG CCT TGT GGA ACA AGT GGT GGA GTC ATG ATC TAT ATT   308

 D  R  I  E  V  V  N  M  L  A  P  Y  A  V  F  D  I  V  R  N    108
GAC CGA ATA GAA GTG GTT AAT ATG TTG GCT CCT TAT GCA GTG TTT GAC ATT GTG AGG AAC   368

 Y  T  A  D  Y  D  K  T  L  I  F  N  K  I  H  H  E  L  N  Q    128
TAT ACT GCA GAC TAC GAC AAG ACT TTA ATC TTC AAT AAA ATC CAC CAT GAG CTG AAC CAG   428

 F  C  S  A  H  T  L  Q  E  V  Y  I  E  L  F  D  Q  I  D  E    148
TTT TGC AGT GCC CAC ACA CTT CAA GAA GTT TAC ATA GAA TTG TTT GAT CAA ATA GAT GAA   488

 N  L  K  Q  A  L  Q  K  D  L  N  T  M  A  P  G  L  T  I  Q    168
AAC CTG AAG CAG GCC CTG CAA AAA GAT TTA AAC ACC ATG GCC CCA GGT CTC ACT ATC CAG   548

 A  V  R  V  T  K  P  K  I  P  E  A  I  R  R  N  F  E  L  M    188
GCT GTG CGT GTT ACA AAA CCC AAA ATC CCA GAA GCC ATA AGA AGA AAT TTT GAA TTA ATG   608

 E  A  E  K  T  K  L  L  I  A  A  Q  K  Q  K  V  V  E  K  E    208
GAG GCA GAG AAG ACA AAA CTT CTC ATA GCT GCA CAG AAA CAA AAG GTG GTG GAG AAA GAA   668

 A  E  T  E  R  K  R  A  V  I  E  A  E  K  I  A  Q  V  A  K    228
GCT GAG ACG GAG AGG AAA AGG GCT GTT ATA GAA GCA GAG AAG ATT GCA CAA GTA GCA AAA   728

 I  R  F  Q  Q  K  V  M  E  K  E  T  E  K  R  I  S  E  I  E    248
ATT CGA TTT CAA CAG AAA GTG ATG GAG AAA GAA ACT GAA AAA CGC ATT TCT GAG ATT GAA   788

 D  A  A  F  L  A  R  E  K  A  K  A  D  A  E  Y  Y  A  A  H    268
GAT GCT GCG TTC CTG GCC CGA GAG AAG GCA AAA GCA GAT GCC GAG TAT TAC GCT GCA CAC   848

 K  Y  A  T  S  N  K  H  K  L  T  P  E  Y  L  E  L  K  K  Y    288
AAA TAC GCC ACC TCA AAC AAG CAC AAA CTG ACC CCA GAG TAT CTG GAG CTC AAG AAA TAC   908

 Q  A  I  A  S  N  S  K  I  Y  F  G  S  N  I  P  S  M  F  V    308
CAG GCC ATT GCC TCA AAC AGT AAG ATC TAC TTT GGC AGC AAC ATC CCC AGC ATG TTT GTG   968

 D  S  S  C  A  L  K  Y  S  D  G  R  T  G  R  E  D  S  L  P    328
GAC TCC TCC TGT GCT CTG AAA TAC TCT GAT GGT AGG ACT GGG AGA GAA GAC TCC CTT CCC  1028

 P  E  E  A  R  E  P  S  G  E  S  P  I  Q  N  K  E  N  A  G    348
CCA GAG GAG GCC CGT GAG CCC TCT GGA GAG AGC CCC ATC CAA AAC AAG GAG AAC GCA GGT  1088

 *                                                               349
TGA                                                             1091

TGCAAGAGGTGGAAATGTTCTCCCATATCAAGATGCGACCCAAGGGGCTAAGTGGGAACAGTGGTTATGTGGACTCGTA  1170

AGATTCACAGAGAATGTGTGCTCTGTTGTGATTCTCTTGTCATAGTCCTGGTTTGCCAGCTGACTACAGGATAGACCCA  1249

GCTGTCTGGCACTCAAACGGTCTCTGCAGCCACAGTTTTATCAAGTATCCTGTATGTGTTCCTTTGTAAACCGGTACTC  1328

ATGAATGAGGGAAAGTCTGATGCTAAGATACTGCCTGCACTGGAATGTCAAACACTATATAACAAGCTGTGGTTTTTAA  1407

AAGCTATTGAATAATGTTTACATTGGTCCCTGAGGACATGTGTGCTCAGACATTCAAGAGCTAGGAGGCCAGAGAGAAG  1486

ACCTTCAGAAAACGGTAAGTTAAAGAAGACAAGTGTCATCAGACACTTGGGACCCGGGCTCTCTTTAAAGTCTAGTCCC  1565

GGCATTCCTCCATGTGATTGACAGCCAGACCTCTGGGTTCCCAGGAAATTATCTTCCAGTTGAATGACCATTTACTTGA  1644

TACAAATTGTACCTTTCTGTTTTTCTAGTCAGGTTGGTGGCCTGCAGGGACGCGTACTTTGCCACCCGACCAGAGGTTC  1723
```

FIG 54 (1 OF 2)

CTCGAAGATATTCCCAATCACTAGTTTATTGCGTTAGGAGACTCAGAGATATAGAAAGCAGCTGAAATTTAAGGGAGAT 1802

AAAGCCTGCACTGCACCAAAGCTACGGGTCCCTGTGTTTCCTCTATTCAGTGATGTCATCAACCTCACTGTCCCAGCCC 1881

ATGTGTGACTAAAGTGCCCGGTTTTAGCCACAGACAACTGCTTAGATGTCACCTCTTGGCTGACCAAAGCTGGGACAGG 1960

GCTTTAACCAGACATAGGAGCAGTGTGCAATTCCTGATTCACTGCACAGTATTATGTCATAATTGCAGGAATTATTTTT 2039

TGTTTTTAAAACTGGATTTGGGGCACATTCATTCACCCCAACACTTCTATCTAAAGGCCAAGGTTCTAGGGCTGCTATG 2118

GTCACTAACACACTGATTCTCCTTAAAGTAATTCTCGAAGTGTGGAACAAAGTGACCGAGACAGCATCCTCAGTCATCT 2197

TTGTCTCCTTCCCTGGGATGCAGATACCGAAGTTGCTTTTCCAACTTTCGCCTCCGCTAGGAGATCAGAAAGAATTCTT 2276

GTGACTTCCTGGGCAGCCATTGAATTCATTTTCCATGAGAAGATGACAGAGTTAGCCTGTGGCTATAGGAGATCATGTC 2355

ATCCAGACCTTTTTGCCCATCACATTAACTTTCCTGGAATATTGTGCTGCACAGGTAGACCTGAATCTGCCCAGCTTGT 2434

TGACAGCTCTTGTGTATACTGTGTTGAAGCCAGACAGAAAAGTAATGGGGCCACTTCTGAAACCTCTCAGCTGTTGATC 2513

TCACAGCAGCTAAAGGGTTGTGCCAAACATTTTATTAAGAAAGTAAAGCCCAGATTTGAATGGGGGTTTTCCCTAGGCC 2592

TTATAGTATAGAGGCATTTGTAATATGGAGAAAATAATTTTTCTCATTTAATTATAGAAATTACCTTCAAACAGATTTT 2671

GTGTTCTTTGGCCCTTCAAATACTGGTGTTACATTGTTGCTGCAGATAAATGATGATTGTCGTGGGATATCTGGATCAC 2750

TGAGCTCTGTGCTTTCATTCCTAGAGATGTTTCTCATTCCCATTTAGTGAAATGCTGTTGCCCCAAAGTGATGGTTGTG 2829

GGATTTCTTACCGGTCATAGGCCCCGGTGAGGAGCAGGGAAGCGCCATTGTGAAAGATTAAAGAAAGCACTTCCACTTG 2908

AGCTCCTTATGGAGTGAGCTTCCCTGTGCCCACTCAGTGAACTAAGTCTGACCATCCTTCAGGGACGTTCCTTTTGGTA 2987

AATATACACTGTAATCTTTAAGTCTAAATTTATATGTGAAAGTTAACTTTTTTTAAAAACCTAAATAAAATTATTTTCC 3066

TATCAAAAAAAAAAAAAAAAA 3087

Fig 54 (2 of 2)

Input file T187Aymue064g11; Output File T187Aymue064g11.pat
Sequence length 2883

```
GTCCAGGAAAAAGCTGCTTGCACTAGGGGCATCCCGCCTGCCTGGTGAAAGGAACCGCAGCACACAGGGTGGGAGGGCT  79

TCCGATTTTAGCAGGGCGGCTTCCGGAAGGCGGAGCTCCAACCCCATTTCCTTTCTCTGGGCTGGTTCTGGCCCAGCTG  158

                                                    M  G  G  A  R  D      6
CACCTGCGTGTGGCCCTGGCTCCTCGGCTCCCTGCAGCTCCGAGGCAGCAGC ATG GGT GGC GCG CGG GAC     228

 V  G  W  V  A  A  G  L  V  L  G  A  G  A  C  Y  C  I  Y  R    26
GTG GGC TGG GTG GCA GCA GGG CTG GTC CTG GGC GCC GGC GCC TGC TAC TGT ATC TAC CGG  288

 L  T  R  G  P  R  R  G  G  R  R  L  R  P  S  R  S  A  E  D    46
CTG ACT CGG GGA CCG CGG CGA GGC GGT CGC CGA CTG CGC CCT TCG CGA TCC GCA GAA GAC  348

 L  T  D  G  S  Y  D  D  I  L  N  A  E  Q  L  K  K  L  L  Y    66
CTA ACC GAT GGC TCC TAT GAC GAT ATC TTA AAT GCA GAG CAG CTT AAG AAA CTT CTG TAT  408

 L  L  E  S  T  D  D  P  V  I  T  E  K  A  L  V  T  L  G  N    86
CTG CTG GAG TCA ACC GAC GAT CCT GTC ATT ACT GAA AAG GCC TTG GTC ACC TTG GGA AAT  468

 N  A  A  F  S  T  N  Q  A  I  I  R  E  L  G  G  I  P  I  V   106
AAT GCA GCC TTC TCC ACT AAC CAG GCC ATT ATT CGT GAG TTG GGT GGT ATC CCA ATT GTT  528

 G  N  K  I  N  S  L  N  Q  S  I  K  E  K  A  L  N  A  L  N   126
GGA AAC AAA ATC AAC TCC CTG AAC CAA AGT ATT AAA GAG AAA GCT TTA AAT GCA CTG AAT  588

 N  L  S  V  N  V  E  N  Q  T  K  I  K  I  Y  V  P  Q  V  C   146
AAC CTG AGT GTG AAT GTT GAA AAT CAA ACT AAG ATA AAG ATA TAC GTC CCT CAA GTC TGT  648

 E  D  V  F  A  D  P  L  N  S  A  V  Q  L  A  G  L  R  L  L   166
GAG GAC GTC TTT GCT GAC CCC CTG AAC TCT GCG GTG CAG CTG GCC GGA CTG AGG CTG CTG  708

 T  N  M  T  V  T  N  D  Y  Q  H  L  L  S  G  S  V  A  G  L   186
ACA AAC ATG ACG GTC ACC AAC GAC TAT CAG CAC CTG CTC AGC GGC TCC GTC GCT GGC CTG  768

 F  H  L  L  L  L  G  N  G  S  T  K  V  Q  V  L  K  L  L  L   206
TTC CAC CTG CTG CTG CTG GGA AAC GGA AGC ACC AAG GTC CAG GTT TTG AAG CTG CTT TTG  828

 N  L  S  E  N  S  A  M  T  E  G  L  L  S  V  Q  V  S  R  L   226
AAT TTG TCT GAG AAT TCA GCC ATG ACA GAA GGA CTA CTG AGT GTC CAA GTA AGT AGA TTA  888

 P  T  R  F  I  S  A  H  I  Q  R  F  *                        239
CCT ACC CGG TTC ATT AGT GCA CAC ATA CAG AGA TTT TGA                              927

CAAATAGATCTGCAAAGGTATGCCCAAAAACATTCACAGGAATTATTTCTGAAGATGAGTATTAAGCATATTTTGTTTT  1006

TTAAAACTTCTCTGTGGCACCAGCAGACTTTCCATCTCTGGCCACTTTGCAGTATTTTTCTGTCACTGCATTTTAAAGT  1085

TTGTTTTTTTTGTGCATGTGTACCTCAGCATTTGCTGAAACAACTGTACTGAGTGAGTCCCCTGTGTGGGCTCGGTCCT  1164

GAGCATTCAGCCAGCACCAGCAAGTTCTTAGTGTTCCCATGGAACTTAGGAGAAGCAACCATGTAACAAATTAGCAAGA  1243

CTGTTGAAAACATGTAACAAACCATTGAAACAGTCCCTGTGCTCTGAAGAAGGCCAGGCGGTGTGAGCCGTCTGCAGAA  1322

ATCGAGCCATCTGCTCCGTCCTGTTACCAGAACTGTGTGTAAGAGCTAATGCTGATTGAACTAATGTGTTCTTACAAAA  1401

ACTGGATAGATCCTAAAGGGGTTGGTTTCCCAAATGGCTACACTCTGGAGTTCCAAAGAAATCTTAGTTTTTCCCCTAA  1480

CAAAACGTCATTTTCACTTGTAACATGGAATAAAAATGAAACATGTCCCTTACGCTTGCCTGGAGTCAGACTTTTACAG  1559

TGTTAACTAATGGATGCTGTTTTAAAATAGGACAGTGACGCTGTTTCCTCTTTCAGGTGGATTCTTCATTCCTTTCCCT  1638

TTATGACGGCCAAGTAGCAAATGAGATTCTTCTTCGGGCTCTTACACTGTTTCAGAATATAAACAACTGCCTCAAAGTG  1717

GAAGGCCGGTTAGCTAATCAGATTCCTTTTGCTAAAGGGTCATTGTTTTTTCTGTTATACGGAGAAGAATGTGCCCAGA  1796

AAATGAGAGCTTTAGCCTGTCATCATGATGTGGATGTGAAAGAGAAAGCTTTAGCAATAAAGCCGAAATTCTGATCGGT  1875

TGCTCCTATTTTTATCAAAGACTCAAACAGTAAGGCAGTCTTAAGTCAGCACACGGGAGCGTTTGCCTGCCTTTAAAAG  1954

GGGTCTTTCAGCCGATGGAGTTAAACAATAAAAGTGAGTGAGCAGCTCTAATCCAACACGATGTTCAAAATTTTAGATT  2033

TTGGAGTAGTTCAGATTTGGGGTTTGGGGATTGAGTAGAGTCTGGAACCTTCCGAGGATGTGGATCATTTACGGGGCAA  2112
```

FIG 55 (1 OF 2)

ACGTTTGGTTATGATCGTGGACAGACTGGCCATGCTCTTCAGGACTATTTGAAGGATTCTAGTGCTAGTGAATGAATAT 2191

GAGGGGCTGTACTGAAGATACTTGCTGAGGTATTTAATGGTTTCCTGACACGAACTGAGTGGCCTGTCTCTGTACAATC 2270

CTAACTCCTGGGAGCATTTGCAGTTGCTCATGAGACAGCGTTAAGTGCTGAGTTGAAGTCTGTTACTGCCACAGCAAGG 2349

ACCTTGTGCCTCAAACCAGTGAATACTGCAAGCTCGAGTCCACCACCAACCCTGCCATGCTGCTTGCAAGTCTGAGCTC 2428

ATCGTGAGACACTGCCTGCAGCATTTCTGATCAGTAGGACTGTACTCCCATTTACATGGAAAGCGTTTTCTTACTGCTT 2507

ACCCCCTTGTGTAAGATACTGCAGAGCACTCCAAGCTTCCACCCACAGGCAGACAGCCCTTTAAAAAAGAGTGTCCTGA 2586

TAAGTCCAGATGGATACATGGAGAAACATACCCATGAGATGGCTGCTTTGAAAGCATGCTGGGAAGCAATGTATTAGGG 2665

TCCCGTGTCTTTTTTTTCTCTCAGTAATGATAAATACACTTATACATGGACAGAACATTTCTAGAACGATTCAGAAAAC 2744

TTCTGGGACTGGGACTAGGGTACATAGATTTCTTTGTGTTCCTGTTTCTACCGTTTGGATTTGTACTGAGCATAAATTG 2823

TATAATTTTTTAATAAAAAGGAAAAATGCAAGGTGTACATAAAAAAAAAAAAAAAAAAA 2883

FIG 55 (2 of 2)

Input file T215AtmX215; Output File T215AtmX215.pat
Sequence length 2744

```
                                  M  E  L  D  R  W  A  Q  L  G  L  V      12
CTCGGTACCGACACAGCAACGGGAAACG ATG GAG CTA GAC AGA TGG GCG CAG TTG GGG CTG GTG      64

 F  L  Q  L  L  L  I  S  S  L  P  R  E  Y  T  V  I  N  E  A      32
TTC CTG CAG CTC CTT CTC ATC TCA TCG TTG CCA AGA GAG TAC ACG GTC ATT AAT GAA GCC  124

 C  P  G  A  E  W  N  I  M  C  R  E  C  C  E  Y  D  Q  I  E      52
TGT CCC GGA GCT GAG TGG AAC ATC ATG TGT AGA GAA TGT TGT GAA TAT GAT CAG ATT GAA  184

 C  L  C  P  G  K  K  E  V  V  G  Y  T  I  P  C  C  R  N  E      72
TGC CTC TGC CCA GGA AAG AAG GAA GTG GTG GGT TAC ACC ATC CCA TGC TGC AGG AAT GAG  244

 D  N  E  C  D  S  C  L  I  H  P  G  C  T  I  F  E  N  C  K      92
GAT AAT GAA TGT GAC TCC TGT CTA ATT CAC CCA GGT TGT ACC ATC TTT GAA AAC TGC AAG  304

 S  C  R  N  G  S  W  G  G  T  L  D  D  F  Y  V  K  G  F  Y     112
AGC TGC CGC AAT GGC TCC TGG GGC GGA ACT CTG GAT GAC TTC TAC GTG AAG GGA TTC TAC  364

 C  A  E  C  R  A  G  W  Y  G  G  D  C  M  R  C  G  Q  V  L     132
TGC GCA GAG TGC AGG GCA GGC TGG TAC GGA GGA GAC TGC ATG CGA TGT GGC CAG GTT CTT  424

 R  A  S  K  G  Q  I  L  L  E  S  Y  P  L  N  A  H  C  E  W     152
CGA GCC TCA AAG GGT CAG ATC TTG TTG GAG AGC TAT CCC TTA AAC GCT CAC TGT GAA TGG  484

 T  I  H  A  R  P  G  F  I  I  Q  L  R  F  G  M  L  S  L  E     172
ACT ATT CAT GCC AGA CCT GGG TTT ATC ATC CAG TTG AGG TTT GGT ATG CTG AGC CTA GAG  544

 F  D  Y  M  C  Q  Y  D  Y  V  E  V  R  D  G  D  N  S  D  S     192
TTT GAC TAC ATG TGC CAA TAT GAC TAT GTG GAG GTC CGC GAT GGG GAT AAT AGT GAC AGC  604

 P  I  I  K  R  F  C  G  N  E  R  P  A  P  I  R  S  T  G  S     212
CCT ATC ATC AAG CGT TTC TGT GGC AAC GAG AGG CCA GCT CCC ATC AGG AGC ACT GGC TCT  664

 S  L  H  V  L  F  H  S  D  G  S  K  N  F  D  G  F  H  A  V     232
TCA CTC CAT GTC CTT TTC CAT TCT GAT GGC TCC AAG AAC TTC GAT GGC TTC CAC GCT GTC  724

 F  E  E  I  T  A  C  S  S  S  P  C  F  H  D  G  T  C  L  L     252
TTT GAG GAG ATC ACA GCG TGC TCC TCA TCC CCT TGT TTC CAT GAT GGC ACA TGC CTC CTT  784

 D  T  T  G  S  F  K  C  A  C  L  A  G  Y  T  G  Q  R  C  E     272
GAC ACC ACT GGG TCT TTC AAG TGT GCC TGC CTG GCT GGC TAC ACT GGG CAG CGC TGT GAA  844

 N  L  L  E  E  R  N  C  S  D  L  G  G  P  V  N  G  Y  K  K     292
AAT CTA CTT GAA GAA AGA AAC TGC TCA GAC CTT GGG GGG CCA GTC AAT GGG TAC AAG AAA  904

 I  T  E  G  P  G  L  L  N  E  R  H  V  K  I  G  T  V  V  S     312
ATC ACA GAA GGT CCT GGA CTT CTC AAT GAG CGC CAT GTA AAA ATT GGC ACG GTT GTG TCT  964

 F  F  C  N  G  S  Y  V  L  S  G  N  E  K  R  T  C  Q  Q  N     332
TTC TTT TGT AAC GGC TCA TAC GTT CTG AGT GGC AAT GAG AAA CGA ACT TGC CAG CAG AAT 1024

 G  E  W  S  G  K  Q  P  V  C  M  K  A  C  R  E  P  K  I  S     352
GGA GAG TGG TCA GGA AAG CAA CCT GTC TGC ATG AAA GCC TGC CGG GAA CCG AAG ATC TCA 1084

 D  L  V  R  R  R  V  L  S  M  Q  V  Q  S  R  E  T  P  L  H     372
GAC CTG GTG AGA AGG AGA GTC CTT TCG ATG CAG GTT CAG TCA AGG GAG ACA CCA TTA CAT 1144

 Q  L  Y  S  T  A  F  S  K  Q  K  L  Q  D  A  S  T  K  K  P     392
CAG CTT TAT TCC ACG GCT TTC AGC AAG CAG AAA TTG CAG GAT GCC TCT ACC AAA AAG CCA 1204

 A  L  P  F  G  D  L  P  P  G  Y  Q  H  L  H  T  Q  V  Q  Y     412
GCC CTT CCA TTT GGA GAC CTG CCC CCT GGA TAC CAA CAT CTG CAC ACC CAA GTC CAG TAT 1264

 E  C  I  S  P  F  Y  R  R  L  G  S  S  R  R  T  C  L  R  T     432
GAG TGC ATC TCG CCC TTC TAC CGC CGC CTG GGA AGC AGC AGG AGG ACA TGC CTG AGA ACT 1324

 G  K  W  S  G  R  A  P  S  C  I  P  I  C  G  K  I  E  S  T     452
GGG AAG TGG AGT GGG CGG GCC CCG TCC TGT ATC CCA ATC TGT GGA AAA ATC GAG AGC ACT 1384

 P  S  P  K  T  Q  G  T  R  W  P  W  Q  A  A  I  Y  R  R  T     472
CCT TCT CCA AAG ACC CAA GGC ACC CGC TGG CCA TGG CAG GCA GCC ATC TAC CGG AGG ACC 1444
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FIG. 5G (1 OF 2)

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 S  G  V  H  D  G  G  L  H  K  G  A  W  F  L  V  C  S  G  A   492
AGT GGT GTA CAC GAT GGT GGT CTG CAC AAA GGT GCA TGG TTC TTG GTC TGC AGT GGT GCC  1504

 L  V  N  E  R  T  V  V  V  A  A  H  C  V  T  E  L  G  K  A   512
CTG GTG AAT GAA CGG ACT GTG GTT GTG GCT GCC CAC TGT GTG ACT GAG CTG GGG AAG GCC  1564

 T  I  I  K  T  A  D  L  K  V  V  L  G  K  F  Y  R  D  D  D   532
ACC ATC ATC AAG ACA GCA GAC CTC AAG GTT GTC TTG GGA AAA TTC TAC AGG GAC GAT GAT  1624

 R  D  E  K  S  I  Q  N  L  R  V  S  A  I  I  L  H  P  N  Y   552
CGG GAT GAG AAG AGC ATC CAG AAT TTA CGG GTT TCT GCT ATC ATT CTG CAC CCC AAC TAT  1684

 D  P  I  L  L  D  T  D  I  A  V  L  K  L  L  D  K  A  R  I   572
GAC CCT ATC CTG CTT GAC ACT GAC ATC GCT GTT CTG AAG CTC CTA GAC AAA GCT CGC ATC  1744

 S  T  R  V  Q  P  I  C  L  A  T  T  R  D  L  S  T  S  F  Q   592
AGT ACC CGT GTC CAA CCC ATC TGC CTG GCT ACC ACT CGG GAC CTC AGC ACC TCT TTC CAG  1804

 E  S  H  I  T  V  A  G  W  N  I  L  A  D  V  R  S  P  G  F   612
GAA TCC CAC ATC ACT GTG GCT GGC TGG AAC ATC CTG GCA GAT GTG AGG AGC CCT GGC TTT  1864

 K  N  D  T  L  H  Y  G  M  V  R  V  V  D  P  M  L  C  E  E   632
AAG AAT GAT ACC TTA CAT TAT GGA ATG GTC AGA GTG GTA GAC CCA ATG CTT TGT GAG GAA  1924

 Q  H  E  D  H  G  I  P  V  S  V  T  D  N  M  F  C  A  S  K   652
CAG CAT GAA GAC CAT GGC ATT CCA GTT AGT GTC ACT GAC AAC ATG TTC TGT GCC AGC AAA  1984

 D  P  S  T  P  S  D  I  C  T  A  E  T  G  G  I  A  A  L  S   672
GAT CCC AGT ACC CCT TCT GAC ATC TGC ACT GCA GAG ACA GGG GGC ATC GCT GCT TTG TCC  2044

 F  P  G  R  A  S  P  E  P  R  W  H  L  V  G  L  V  S  W  S   692
TTC CCA GGC CGA GCA TCC CCC GAG CCA CGC TGG CAT TTG GTG GGG CTG GTC AGC TGG AGC  2104

 Y  D  K  T  C  S  N  G  L  S  T  A  F  T  K  V  L  P  F  K   712
TAT GAC AAG ACA TGT AGC AAT GGC CTA TCC ACA GCC TTC ACA AAG GTG TTG CCG TTC AAA  2164

 D  W  I  E  R  N  M  K  *                                      721
GAC TGG ATT GAG AGA AAC ATG AAA TGA                             2191

ACCAGCCACAAGGCCACTGAGAAGCCTTTTCCTAGCATCCGTCTGTACATATGTTGTATAGAACAATGCGGGCCTGAAG  2270

TGTAATTTTGCCCACCATCTTGGCTACTGAAAGGCTCCTGGTTTCAGGGACTTATCTCAATAGAGGGTGAACAGAGTTT  2349

ACTTCATCAGGGAACTGTCTCCCTGACTGCTTGGGAATCATCTAAAAGATGCCAGGTCTTGCAACAACTGGATTTCTTC  2428

AAAGAAGACCATGTGACTAGAAGGAGAACCTCTTGCTCCTGCTCCACTCAGAGTGATGTGACTGTCAATCAGTTTGGGT  2507

TGAGAAGGTTGATTTGGGGAGGCCTGGGCTGCACCTGGCTTCTGTCAAAGTTCCAAAGAACAAACAACTTAGACTAGCC  2586

CAGGGCAAAGGAGATTGGGTGTGGCACCCTGTGTAAATTGTCACAAGATTGTCTGATCCTTTCCCTTTCCAATCTTCTG  2665

TACACATTTCAATAAAACAAGGTCTGCTCCCTGACCTACCAAACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  2744

TACACATTTCAATAAAACAAGGTCTGCTCCCTGACCTACCAAACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  2744
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FIG. 5C (2 of 2)